

THE MYELOMA:

ITS CYTOLOGY, BIOCHEMISTRY AND CLINICAL FEATURES

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T H E   M Y E L O M A ;  
ITS CYTOLOGY, BIOCHEMISTRY AND CLINICAL FEATURES

The diagnosis of myeloma has been comparatively rarely made in Edinburgh according to the records of the past twenty years. I have recently seen seven examples of this disease and I propose to analyse these cases and the cases diagnosed as myeloma in the Royal Infirmary so far as the meagre data will allow.



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## DEFINITION

Like so many diseases of unknown aetiology, the synonyms for myeloma are numerous, the name applied depending on the writer's opinion of the causation of the disease. The first report was made by Macintyre (1850) and the name of mollities and fragilitas ossium was used by him. It is as well to mention these names, but it unnecessary to quote the list of their originators. Such terms are used as myeloma multiplex, osteomyelitis maligna, lympho-sarcoma multiplex ossium, sarcoma multiplex ossium, pseudoleucaemia myelogenes, ostitis sarcomata, lymphadenia osseum, endothelioma intravasculare, myelosarcoma, erythroblastoma, erythrocytoma, plasmoma malignum, myeloblastoma, lymphosarcoma, lymphadenoma, hyperplasia of the osseous medulla, systemic sarcomatosis of the medulla, different forms of sarcoma, general lymphadenomatosis of bones, myelopathic albumosuria, Kahler's disease, Huppert's disease, myelomatosis, multiple myelomata, and plasmacytoma. These twenty-six names in themselves show the state of ignorance which is associated with this most interesting disease, but a glance at the terminology employed at once suggests to the reader that probably more than one pathological entity is present and that more than one cellular unit is responsible for similar morbid anatomical/

anatomical and clinical pictures. Then it is necessary to define the limits of the disease which I propose to discuss.

I prefer to use the term myeloma for the individual tumour and if the tumours are multiple then the name multiple myelomatosis is logical, and by this term is indicated a more or less widespread multiple neoplastic affection of the osseous medulla, leading to destruction of the compact and spongy tissue of bony substance. Metastases may occur, and the tumours may indeed not affect the skeleton at all but be single or multiple and confined to the lymphatic tissue, the name extra-osseous myeloma then being used. This latter manifestation is very rare.

There are various cells in the osseous medulla and from a study of these cells and an histological comparison to the predominant or only tumour cell type have come the different opinions of which is the kind of cell responsible for the growth. Again, by a glance at the synonyms quoted, it is clear that all the marrow cells in turn have been held responsible and it is quite possible that such conditions may exist, as for example we are acquainted with the reticulum system of cells in the marrow and the malignancy known as reticulum cell sarcoma, and we know of the myeloblast and the somewhat rare chloroma. Thus, it would appear, a myeloma may have a choice of cell/



cell type and tumours are reputed to be composed of erythroblasts, erythrocytes, myeloblasts, myelocytes, lymphoblasts, lymphocytes, plasma cells and perhaps others. I am not able to deny these possibilities, however much I may doubt them. Vance (1916) gives five types of myeloma and quotes the cases recorded in the different types. I shall confine my field to the cases at my disposal diagnosed as myeloma and drawn mainly from the records of the Royal Infirmary, Edinburgh, plus a few cases from outside sources to which due recognition will be accorded.

As most of the cases in my series show the predominant malignant tumour cell to be morphologically similar to a plasma cell, the word plasmacytoma is frequently used. This tumour then is a form of myeloma and the words may be interchangeable.

Mention has been made of extensive osseous involvement and it will thus not be difficult to understand that secondary to that, other systems may be involved; among these the central nervous system, the thorax and lungs, the liver, kidneys and spleen and the peripheral blood may all singly or in combination add to the very compositive picture of a disabling and fatal disease.

In my search through the records in the Royal Infirmary I found 40 in which the term 'myeloma' was used. On analysis 15 of these clearly were not the/

the disease I wished to discuss, the word myeloma being loosely used for tumours such as giant cell tumours of bone, sarcoma, various forms of epulis, and lymphatic or myeloid leucaemias where some sort of tumour growth was observed, and finally in cases where there was found clinically some vertebral collapse and the diagnosis of myeloma was made by the process of elimination, no X-ray photograph or biopsy being taken to substantiate the opinion. This leaves 25 cases from the Royal Infirmary alone which I wish to discuss where the final diagnosis of myeloma was made, either correctly or incorrectly. Four cases of myeloma are added which are not in the Infirmary records.

#### HISTORY & GENERAL REVIEW.

The disease now known as myeloma was first put on medical record in 1850 by Macintyre, though he observed it in 1845. This same case was also seen by Bence-Jones at that time, who was engaged in examining the patient's urine about which he later gave a full and detailed report. This mentions 'animal matter' which subsequently became known as Bence-Jones albumose, protein, proteose or bodies. Microscopical examination of the tumour was performed by Dalrymple (1846) on two affected ribs, and he describes

"nucleated/



"nucleated cells ..... The greater number are round, some are oval, others more irregular and pointed at one extremity. The round and smaller ones are about one and a half to twice larger than the average blood cells and, for the most part, contain a single faint grey nucleus with a very bright and distinct nucleolus ..... frequently two included nuclei ..... often three nucleolated nuclei ..... once or twice I have seen indications of a fourth included nucleus."

This describes the plasmacytoma cell about which this thesis is so much concerned.

Though these three men were the pioneers, their work seems to have been forgotten by, or unknown to, later students, and twenty-seven years later Rustizky (1873) was given the credit for an histological study of the disease and Kahler (1889) was the first to connect the appearance of Bence-Jones bodies with multiple myeloma. It was Kahler who was really responsible for drawing attention to this disease, and between 1848, when Bence-Jones published his report, and 1889 only 5 probable cases of multiple myeloma are found in medical literature.

During this period the eyes of the morbid anatomist were not dimmed and though no cases were published, Rokitansky (1856) described the presence of many small tumours in the spongy tissue of the bones of the trunk, gradually uniting to form large tumours, and Förster (1863) was impressed with the frequent appearance of fragility of the bones due to cancerous deposits, thus producing a condition often/

often mistaken for osteomalacia, and, like Volkmann (1882) later, he referred to a diffuse cancerous infiltration of the bone medulla filling the reticular spaces of the spongy tissue causing skeletal deformities similar to what occurs in osteomalacia. He also drew attention to the severe pains associated with the disease, sometimes mistaken for rheumatism. In all probability these descriptions referred to myelomata.

Rustizky gave us the name of multiple myeloma, his choice being made because the tumours were considered by him to be due to hypertrophy of the osseous medulla. Histological detail is surprisingly wanting in the early cases.

In 1897 Ewald reported on a tumour removed from a man aged 62 years, consisting of plasma cells, this being the first case of a solitary plasmacytoma. Bradshaw (1898) made the first antemortem diagnosis, unverified by autopsy but almost certainly correct.

Kahler's work produced a stimulus which was felt mainly in Italy, and the works of Bozzolo in 1897 and 1898 produced many case reports, and from then on <sup>an</sup> ever increasing spate of publications in one way or another related to myelomatosis may be found in the literature, and though the English works are first in this field, German contributions are much more numerous.

Calcium/

Calcium metastasis was found in the kidneys by Schur and Löwy in 1900, and in 1904 Ribbert described the first example of the erythroblastoma form of myeloma. By 1909 more interest was being taken in the cytology of myeloma, and in this year Weber and Ledingham divided myelomata into lymphocytic, myeloblastic, myelocytic, erythroblastic and plasmacytic cell types, and mixed forms may be added. In 1906 Aschoff had reported the presence of plasma cells in the blood in cases of myeloma.

The biochemists now joined in, and Hopkins and Savoury (1911) reckoned hypercreatinuria to be a constant finding in myelomatosis. Rosenbloom (1912) found that osseo-albuminuria could produce Bence-Jones albumose and in 1917 Glaus noticed that the tumour cells contained crystalline deposits. Hopkins and Savoury were also the first to notice the rapid rouleaux formation so that the red cells could not be counted. Soon afterwards it became evident that other organs in the body might be affected without necessarily being invaded by tumour growth, and in 1920 Mannhauser and Krauss describe the kidneys in their case.- the main lesion was a degeneration of the tubular epithelium and they called the condition a nephrosis.

By 1928 there were sufficient cases on record for Geschickter and Copeland to write a review of what was known about this disease, adding 11 of their own cases/



cases and thus bringing the total up to that date to 426.

No treatment was ever of any use, until in 1930-31 Coley claimed success in 4 out of 13 cases by using the toxins of erysipelas and bacillus prodigiosus together with radiation. No one else has attempted this treatment and at the present day radiation is used alone and the myeloma is found to be very sensitive and to react successfully, but there is always a recurrence with a fatal result.

So far only those of middle age were known to be afflicted, but in 1930 Jacoby published the first case of myeloma in a child, aged 8 years, diagnosed by X-ray and verified by autopsy. All the vertebral bodies were affected and also the lumbar spines. The X-ray photograph is a remarkable one.

A more thorough investigation of the kidney pathology was made by Bell (1930) and renal insufficiency for various reasons to be discussed later was found to be common.

Experimental work was also keeping pace, much of it due to the investigations of Magnus-Levy into the origin of Bence-Jones proteose, and the condition of hyperproteinemia; the experiments started at the beginning of the century. More will be said of this later. In the experimental line it is worthy of mention that Furth (1933) found a filtrable virus capable of producing in chickens myelomatosis with/

with or without leucaemia.

The biochemistry of myeloma has gradually been attracting more and more attention for the past two decades, and the work done during that time is freely quoted in this thesis.

And so we come to the present day when, though the recorded cases of myeloma are only about a thousand, it has become a well recognised disease and has been met by numerous clinicians of all kinds and by pathologists who are perhaps not so enthusiastic as to publish what now can only be reckoned as a not uncommon disease.

A good summary of the disease can be obtained from the publications of Geschickter and Copeland (1936) and of Atkinson (1937).

The cases in my series fall into eight groups; all these cases were diagnosed as myeloma.

Group I - Twenty cases all of which have been histologically proved to be of the plasmacytoma variety of myeloma. Of these cases 1 to 8 have been brought to autopsy. In 9 to 20 biopsy and/or sternal puncture has been the method of proof.

Group II - Case 21 stands alone. It is claimed to be one of a plasma cell tumour localised to the tonsil - an extramedullary plasmacytoma.

Group III - Two cases of plasmacytoma showing leucaemic manifestations - Nos. 22 and 23.

Group IV - Case 24. This is considered to be one/



one of plasma cell leucaemia without myelomatous formation within the definition of the disease.

Group V - Two cases diagnosed as myeloma of the myeloblastic type. No blood films were available and it is difficult to establish them definitely as myelomata. They may be cases of myelogenous leucaemia with chloromatous manifestations - Nos. 25 and 26.

Group VI - Two cases diagnosed as myeloma, myeloblastic and myelocytic in type. Here there is more evidence for taking these cases to be myelogenous leucaemias, with nodular formation, i.e. chloroma - Nos. 27 and 28.

Group VII - The diagnosis is entirely radiological; the photographs show the typical lesion of myeloma - Nos. 29 - 32.

Group VIII - Finally 3 cases, Nos. 33 - 35, diagnosed as myeloma on radiological evidence mainly, supplemented by biochemical indications, as in Case 34, disproved histologically.

There are thus 29 cases of myeloma open to discussion which are more or less definite, three misdiagnosed cases, two cases of chloroma and one supposed plasma cell leucaemia.

## AUTOPSIES OF CASES OF PLASMACYTOMA

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### Case 1

Robert J.            Aet 43.            Post Office Clerk.

Admitted - 30.9.30.    Died - 4.11.30.

Complaint - Pain in the legs, sciatic in type.

Abstract of Case - The sciatica had been recognised for two years but no cause found until 2 months before death an inoperable pelvic tumour was found.

Abstract of Autopsy - The body was that of an emaciated subject. A tumour grew from the front of the sacrum and the sacro- iliac joint on the left side. It was rounded, fixed to the bone, and firm.

Apparently there were no other obvious tumours seen, but a systematic examination of the skeleton was not done.

Microscopically - The tumour is typically of the plasma cell type, complete with eccentric nucleus and single nucleolus and an amphophylic cytoplasm with a clear paranuclear area. (Fig. 1).

Spleen was enlarged, due to congestion.

Lungs - Bronchitis and bronchopneumonia.

No other relevant points are recorded.

Comment -            Plasma Cell Myeloma.  
Pain and loss of weight.

### Case 2

Robert F.            Aet 45.            Painter.            Married.

Admitted - 22.12.33.    Died - 31.12.33.

Complaint - Pain in back, 10 weeks.  
Breathlessness, 2 days.

### Abstract of Case Records -

The patient has had lumbar pain, off and on, since early in October, 1933, and has been in bed for about the last 7 weeks. He was gradually getting better until 2 days before admission when he/

he suddenly became breathless and developed a cough with frothy sputum.

Temperature 100.4 °F.

B.P. 145/86. Wasserman reaction - negative.

X-ray showed compression of body of 6th dorsal vertebra.

C.N.S. - Arm, knee and ankle jerks increased; plantar response doubtful. No motor nor sensory loss; cranial nerves normal.

Urinary System - S.G. 1020. Albumen +. Bence Jones protein not looked for.

Respiratory, Circulatory, Alimentary, Haemopoietic and Lymph Glandular Systems carefully examined, but nothing relevant found.

### Abstract of Autopsy

The body was that of an emaciated, middle-aged male. Routine examination of the organs was merely a series of negative findings until the spine was examined.

Spine - The bodies of the 4th, 5th, 6th and 7th dorsal vertebrae were unduly soft and slightly wedge-shaped. The body of the 6th dorsal vertebra was replaced by a soft, white growth which had the naked-eye appearance of a neoplastic deposit.

No primary site for a metastatic deposit could be found.

Section of Vertebrae - The section of the 5th dorsal vertebrae clearly shows several nodes of myelomatous growth circular in outline (Fig. 3). These centres have not fused and the vertebra has not collapsed. The 6th vertebra (Fig. 4) has collapsed, however, because its body is entirely replaced by neoplastic tissue. An effort at strengthening the bone can quite clearly be seen in the upper part of the photograph where the intervertebral disc is encroached upon and there is new bone formation.

Section of Bone Marrow - Only myeloma tissue is present in the section. The cells are in sheets with strands of connective tissue isolating 20 cells or so at a time. Each cell is round with a slightly eccentric round nucleus which in the majority of cases contains a central nucleolus. In the nucleus the chromatin tends to collect in blobs at the periphery of the nucleus. This is typical plasma cell type and the chromatin grouping is well shown with Heidenhain's iron haematoxylin stain (Fig. 2).

### Comment -

There is a relatively short history. Only the vertebrae seem to be affected and compression of one of them caused but little nervous disability. The malignant cell is the characteristic plasma cell variety. The condition was not recognised by X-ray. Pain.

Case/





around this and the cord was not compressed. (Fig. 6). X-ray examination of the isolated spine showed excessive decalcification of the vertebral bodies and as a result of softening the intervertebral discs had expanded and produced little herniations into the bodies, especially in the lumbar region (Fig. 5).

The Sternum had been equally infiltrated and the medulla is reduced to a soft, greyish, pulpy mass with patchy haemorrhage.

Microscopically - In the vertebrae and the sternum the bony trabeculae have been completely replaced by a diffuse infiltration of cells resembling plasma cells. The vascular framework alone remains with a few minute spicules of decalcified bone. There is haemorrhage in the sternum tumour tissue.

Comment - Diffuse damage in vertebral column.  
Partial recovery after initial symptoms.  
Plasma cell myeloma.  
Raised blood calcium, showing destruction of bone.  
Pain, loss of weight and anaemia.

#### Case 4.

John S.                      Aet 61.                      Shale miner.

Admitted - 5.1.35.                      Died - 22.1.35.

Complaint - Pain in the chest behind the sternum since 25th May, 1934 (8½ months).  
Pain down right side of abdomen, 5 weeks.

Abstract of Case History - Before the accident to be described occurred on 25th May, 1934, he had some mild praecordial pain subsequent to his walking into a tree. There was no recurrence of the pain. In May he was lifting a hutch full of ashes (6 cwt.) along with other men and boys, when a boy who was helping him slipped and he had to take the sudden extra weight. There was no question of the hutch or anything hitting him. He felt a sudden jerk in the small of his back. This did not lay him out and he could still lend part of his weight in support, but a sharp pain was felt at the time the accident occurred. Bending thereafter hurt him and he rested for 11 weeks and, though not quite well, tried to break himself in gently until he carried rails on his shoulders, when he felt the pain in the back again, accompanied by pain in the mid-line of the chest in front. There followed some pain on the right side and latterly an almost constant pain to/



to the right side of the abdomen.

Examination - The points of interest are that pressure on the sternum caused intense pain, as did also pressure on the upper ribs. No such tenderness was found over the spine.

Routine examination of Chest, Abdomen, Nervous System and Glandular System gave normal results. There is no record of blood or urine examination.

Wasserman Reaction - negative. B.P. 120/80.

X-ray Report - Compression fractures of 1st and 2nd L.V.

The cause was not indicated.

The patient developed bronchitis, and died on 22.1.35.

#### Abstract of Autopsy -

The body was that of a well developed, well nourished male.

Skeletal System - Numerous cystic cavities were present in the cancellous bone of the sternum, several ribs, the vault of the skull, right femur and several vertebrae. The appearance suggested cystic osteitis fibrosa.

Vertebral Column - The anterior surface of the 1st lumbar vertebra has an angular depression with infolding of the periosteum consistent with an old compression "fracture". There is little naked-eye evidence of separatory thickening of bone. The cancellous bone is congested below, behind and to the left of the fracture.

Areas whose appearance is suggestive of osteitis fibrosa occur in the bodies of thoracic vertebrae 6, 9, 10 and 11, and to a lesser extent in lumbar 3; also in the spinous processes of thoracic 9 and 10. A tumour mass 4 cm. in diameter is present below the spinous processes of the 3rd lumbar, extending downwards and to the left over the left transverse process of the 4th. Anteriorly, it bulges into the spinal canal, displacing the nerves of the cauda equina, but so far as can be judged, not grossly compressing them. They would, however, be stretched to some extent.

In the X-ray of the resected column there is a definite discontinuity of the cortical bone on the lower side of the 3rd spinous process, and this discontinuity is in relation to a vague shadow extending down to the transverse processes of the 4th lumbar. Judging by the X-ray picture, the bony structure of these is unimpaired.

Small tumour masses are present in the bodies of the 6th, 8th and 9th thoracic vertebrae and 4th and 5th lumbar, the latter being by far the largest and situated in the mid-line immediately deep to the anterior surface of the bone. Similar small masses also occur in the spinous processes of thoracic/

thoracic 5th, 6th and 11th and in lumbar 1st, 2nd and 4th, as well as the larger mass in relation to lumbar 3.

Microscopically - The cells of the tumour mass are all the same type, packed tightly together with practically no connective tissue support. They are typical plasma cells complete with eccentric nucleus, cart-wheel pattern chromatin and a clear area in an amphophilic cytoplasm, (Fig. 7). The nucleolus, though present, is not a consistent feature. Similar masses of various sizes, together with areas of more diffuse plasma cell infiltration, occurred in all the vertebrae recognised above as pathological. There was no evidence of osteitis and what appeared to be this to the naked-eye was haemorrhage. There was no vertebral collapse so long as the plasma cell growth was nodular, but when diffuse, collapse occurred.

Routine examination of the respiratory organs, circulatory, alimentary, genito-urinary, central nervous and endocrine systems revealed nothing relevant. The parathyroids were normal.

Comment - The myeloma cell is of plasma cell type. Vertebrae and ribs are alone affected. Lumbar 3 is the oldest lesion and the disease apparently started here. There are no metastases outside the skeleton. The naked-eye appearance was similar to osteitis fibrosa. The condition was not definitely diagnosed by X-ray as a myelomatosis. Pain.

#### Case 5

Mrs Jean T.                      Aet 48.                      Housekeeper.

Admitted - 5.7.35.      Died - 15.10.36.

Complaint - Pain in back and chest.      Weakness generally.

Abstract of Case Record - In November 1934 the patient complained of pain affecting the upper part of the back on both sides of the spine, spreading to the scapulae and also the front of the chest over the upper sternum. It was a dull ache, worse at night and when she exerted herself. It had been variously diagnosed as rheumatism, pleurisy and neuritis. At the same time she felt weakness/

weakness in the back and it began to bend, while a ridge appeared across the chest in front. While in bed she feels in good general health and has not lost weight.

Thorax - There is a marked scoliosis convex to the right affecting the lower cervical and upper thoracic portions of the vertebral column, and kyphosis affecting the lower thoracic portions. Over the front of the chest, halfway down the sternum there is a ridge of bone  $1\frac{1}{2}$ " deep running right across the sternum almost to each side of the chest wall. Below this the sternum is hollowed out and then the anterior ends of the lower ribs appear to have bunched together and projected forwards. The effect is as though the thorax had been telescoped from above downwards.

X-ray of the skull showed a mottled appearance suggestive of malignant deposits.

Examination of Calcium Balance, after 3 day control period -

18.7.35 - <u>Calcium</u>	Total intake	0.433 G.
	Total output	4.326 G.

<u>Phosphorus</u>	Total intake	1.932 G.
	Total output	2.155 G.

For 3 day period -

Before balance -	Blood Calcium	9.2 mgm.%. Blood phosphorus 4.4 mgm.%. After balance -
	Blood Calcium	9.3 mgm.%. Blood phosphorus 4.0 mgm.%. 1.8.35 - Calcium
		9.43 mgm.%. 9.37 mgm.%. 27.11.35 - Phosphorus
		3.6 mgm.%. Phosphatase 43.9 Calcium 9.1 mgm.%. Wasserman Reaction -ve. No palpable tumours. Five months later she was tripped up in the street and could not rise because of pain in the left hip, and she was found to have signs of fracture. She had lost a lot of weight this time but still had a good appetite. The skeletal changes were much the same. Further clinical examination revealed nothing positive/



positive except in the urine.

Urine - This was usually heavily loaded with albumen varying from 5 - 17½ G. per litre a day, and Bence Jones protein was found regularly.

Gradually the condition deteriorated.

31.5.36	Phosphorus	3.0 mgm.%,
	Phosphatase	37.5
	Calcium	10.0 mgm.%,
18.8.36	Blood - R.B.C.	2,570,000
	W.B.C.	6,200
	Hb.	48%
	C.I.	.8

The patient had much pain towards the end, and died 15.10.36.

X-ray Reports (after her accident) -

30.5.36 - There is a fracture of the left pelvis with protrusion of the acetabulum. There is a generalised rarefaction of the bones of the pelvis and upper femora. Small cystic areas are seen. The bone alteration of the femora extends down into the shaft. Similar changes are present in the upper end of the right humerus, and in the middle of the shaft. There is a marked rarefaction of the spine with compression of the bodies and bulging of discs into them. Marked deformity is present with kyphosis in the mid dorsal region. (Fig. 9).

Diagnosis - Osteitis fibrosa cystica, probably secondary to parathyroid disease

24.7.36 - Examination of the pelvis. Changes in the bone structure of the left innominate bone and upper end of the femur are due to multiple myelomatosis and the skull changes are similar. (Fig. 8).

Abstract of Autopsy

The body was that of a thin, middle-aged female.

Osseous System - The following bones were removed, all showing characteristic evidence of multiple myelomatosis -

Skull cap, sternum, ribs, both humeri, both femurs, the pelvis and vertebral column.

Some of these are shown in the photographs (Figs. 10-15).

Microscopically/

Microscopically - The femur was examined and there was a dense infiltration of myeloma cells of the typical plasma cell variety, complete with clear area in the cytoplasm, eccentric nucleus, nucleolus and clumped chromatin.

Kidneys - Average size and shape, but very pale; the fibrous striae were increased. The sub-capsular surface was coarsely granular. The appearance was like a chronic parenchymatous nephritis.

Microscopically - The interstitial tissue is diffusely increased and here and there are indefinite patches of round cell infiltration in which no plasma cells are recognisable. The arcuate vessels are thickened but no gross change is seen in the efferent glomerular vessels. The tubules vary considerably in size; some are dilated and may contain a plug of polymorphs - acute pyelonephritis, others are atrophied, due to the chronic renal lesion itself, mixed arterial and parenchymatous in origin, or to the enormous quantity of large hyaline casts. Several of these casts are apparently surrounded by cells like the lining epithelium of the tubule (Figure 16), or more flattened phagocyte-like cells (Fig. 17) which fuse together and form giant cells (Fig. 18). These casts stain yellow with Azan and may be Bence Jones protein possibly treated as foreign bodies by giant cells, if such they are.

The glomeruli are but little fibrosed, but a few are diminished in size. The general picture is one of chronic pyelonephritis with a superadded acute manifestation. The polymorphs in the cast laden tubules do not seem to enter into the giant cell formation. The atrophy present then is mainly due to the chronic parenchymatous condition, though the obstructive element caused by the casts must have greatly added to it.

Spleen appeared normal to the naked eye, but microscopically numerous cells undistinguishable from the type of myeloma cell in this particular case were seen in the sinusoids (Figure 19).

Routine examination of the other organs of the body showed nothing relevant.

Comment - Plasma cell type of myeloma.

Bence Jones protein passed in large quantities in the urine.

Possible Bence Jones casts causing atrophy to the tubules and giant cell formation round the casts.

Increase of phosphatase.

Pain, loss of weight and anaemia.

## Case 6

William N./



William N. Aet 48.

Admitted - 18.6.36. Died 21.6.36.

Complaint - Retention of Urine.  
Paralysis of the Legs.

Abstract of Case Record - The patient has been bed-ridden for 12 months, suffering from rheumatoid arthritis and chronic nephritis. On 15.6.36 he had acute retention. On admission he was very ill and it was found that he had a flaccid paralysis of both legs and a distended bladder. There was much pus in the urine. He developed chest complications and died on 21.6.36.

Abstract of Autopsy

The body was that of a sparely built, emaciated, middle-aged male, whose lower limbs were much atrophied. There was a subcutaneous nodule over the sternal angle, yellow-white on section.

Osseous System - The ribs and sternum fractured with great ease. The marrow cavities of the ribs were enlarged and in places the ribs were reduced to a mere shell which gave way under the fingers. The soft tissue occupying the marrow spaces was of a yellowish red colour.

The sternum was similarly affected. The interstices of its spongy bone were enlarged and the outer bony capsule was reduced to a thin shell. The marrow here was also of a yellowish red colour and soft consistence.

The bodies of the vertebrae were similarly affected. Their substance was unusually soft and practically gave way under the fingers. The soft tissue occupying the spongy bone of the vertebral bodies was reddish in colour and here and there, in addition, were fairly large nodules of yellowish white tissue. The body of the 10th dorsal vertebra was enlarged by the presence of nodules in its substance and the spinal cord had been compressed by this bone.

Nodules of similar tissue were found in the adjacent spinal muscles.

Examination of the femur at the middle of its shaft showed no bony affection, but the yellow fat was replaced in part by red marrow.

Microscopically - Sections of vertebra, sternum and ribs show the proliferating cell to be of the plasma cell type. There is a clear cytoplasmic area, but the nucleus has not a cartwheel appearance, though the single central nucleolus is clear (Fig. 20). Through the tumour mass hyaline substance is present. This gives a clearly positive reaction for amyloid with/

with the congo-red stain (Fig. 21).

Kidneys were both above average size, rather soft in consistence and on section showed yellowish, congested surfaces in which cortex and medulla were well differentiated. Each capsule stripped readily exposing a granular surface - the granules being pale yellow and the intervening tissue red.

Microscopically - There is some thickening of the arterioles and in the cortex subcapsular wedges of atrophied tissue are frequently seen. Some isolated glomeruli show fibrous crescents, but there is only mild generalised increase in fibrous tissue. There are many casts staining orange with a rather too red Azan and the tubules containing them are atrophied; in these parts infiltrations of round cells are seen. These may be Bence Jones casts, but are more likely to be casts formed from the arterio-sclerotic changes and in their turn assisting and in some cases causing the atrophic condition present.

Comment - The myeloma cell is more the plasma cell type, though the chromatin picture is not quite the typical one.

The case was considered one of chronic nephritis clinically; this indeed is the main kidney lesion, any complication of myeloma being very secondary.

There is amyloid in the marrow.

### Case 7

William D. Aet 69.

Admitted - 19.4.37. Died - 12.5.37.

Complaint - Pain in the chest for 2 days.

Abstract of Case Record - The patient's first symptoms were severe headaches over the frontal and temporal regions, starting suddenly at night and lasting for 2 days, gradually abating. He was inclined to vomit. Three weeks later he felt a sharp pain in the chest, cutting in character and intermittently present, depending on how he moved, localised to the praecordium. Since this last pain appeared he has slept little.

Previous history and family history - nothing relevant.

On Examination the patient was found to be incontinent but routine examination of all the systems revealed no other abnormality, beyond a trace of albumen in the urine.

By X-ray the diagnosis of multiple myelomatosis was made and this was verified by sternal puncture at the level of the 4th rib. The marrow was difficult to obtain as probably there was replacement by firm/

firm myelomatous tissue. The needle was inserted with unusual ease. Ninety-eight per cent of the cells were mononuclears, the predominant type having an eccentric nucleus with a single round nucleolus and a rather fine chromatin mesh. There was a cytoplasmic, pale area beside the nucleus. These are myeloma cells of the plasma cell type.

#### Biochemistry. Blood Examination.

23.4.37 Serum Calcium 10.6 mgm.%.  
Phosphorus 3.9 mgm.%.  
No Bence Jones protein detected.

4.5.37 Serum Calcium 9.7 mgm.%.  
Phosphorus 4 mgm.%.  
Phosphatase 140 Modified Kay.  
Calcium 7.3 mgm.%.  
Calcium

The patient began to pass pus in the urine, rapidly deteriorated and died on 12.5.37.

#### Abstract of Autopsy

The body was that of a well developed, sparsely nourished, elderly male.

Skeletal System - Skull: In the vault were a number of rounded areas of bluish discolouration. These were flush with the surface and did not show any porosity when the skull cap was viewed by transmitted light. The posterior clinoid processes were infiltrated.

Bones - The ribs fractured easily on pressure and their marrow consisted of a gelatinous substance of greyish colour. The left clavicle was removed, and in doing so the acromian process fractured easily. Its marrow had the same appearance as that of the ribs. The sternum was also fractured, but whether this was ante or post mortem could not be decided.

The marrow in the middle of the femur was replaced by active marrow of a reddish yellow colour.

Microscopical Section of Bone Marrow - The marrow is very active, and in the section is a small myelomatous nodule, surrounded by an area of congestion. The cells of the nodule are like the plasma cell, having a definite paranuclear halo. The chromatin of the nucleus has not the typical clustered picture, but a more fine meshwork. The nucleus is eccentric. The cell then is identical with that found at sternal puncture. (Fig. 22).

Ribs/



Ribs - Decalcified specimens showed a similar type of cell.

Spleen was twice its normal size, moderately firm in consistence and, on section, had a firm, red surface.

Microscopically - The pulp was congested and scattered in clumps in the sinusoids were myeloma cells similar to those described above, but no tumour formation was seen (Fig. 24).

Kidney - There was an extensive pyelonephritis and much fibrosis of the parenchyma.

Pituitary - This gland was  $1\frac{1}{2}$  times enlarged, entirely due to the posterior lobe.

The posterior clinoid processes were soft and replaced by gelatinous tissue.

Microscopically - Almost the entire posterior lobe was infarcted, but no myeloma cells were seen (Fig. 25). The infarction was probably caused by the myelomatous infiltration of the clinoid processes obstructing the pituitary blood supply.

There were no other relevant findings in Cardiovascular and Respiratory Systems, the Alimentary Tract, Liver and Central Nervous System.

Comment - Quick death from intercurrent infection

7 weeks after initial symptoms.

Diagnosis clinically by X-ray and sternal puncture.

Myeloma of plasma cell type.

Increased phosphatase.

Pain and loss of weight.

### Case 8

Ian C.            Aet 55.            Schoolmaster.

Admitted - 18.9.39.    Died - 30.9.39.

Abstract of Case Record - The patient had some months of progressive and increasing weakness, anaemia and, in the last six weeks, a neuritic pain in the buttock region, not the true sciatic type. There was considerable hypertension. B.P. 170/100, and he was obviously seriously ill and grossly anaemic. There was a canter rhythm of the heart, albumen in the urine, which had a maximum specific gravity of 1010 and a maximum urea of 0.9%. Blood urea 58 mgm.%. The severe anaemia was considered characteristic of bone marrow intoxication due to chronic uraemia and a provisional diagnosis of myocardial and renal failure secondary to long continued essential hypertension was made.

Blood/

Blood Count - Hb. 15%.  
 R.B.C. 3.13 millions.  
 C.I. .81  
 W.B.C. 9,000  
 Retics. 1.8%.

The film showed a microcytic hypochromic anaemia with an occasional normoblast.

Sedimentation Rate - 142 mm./hour.

X-rays - In view of the autopsy findings it is worth recording that the skeleton was X-rayed and no tumours or fractures found. There was osteoporosis. (Figs. 27-32).

#### Abstract of Autopsy

The body was that of a man of early middle age, of tall build, poorly nourished but not emaciated. Moderate oedema of feet.

Vertebral Column - The vertebral canal at the level of lumbar vertebrae 1 to 3 was filled up by an elongated mass of tumour tissue of homogeneous greyish yellow colour and rather firm consistence. This tissue almost encircled the cord (lumbar enlargement), but the bulk of it was on the left side. The cord was obviously compressed. The tumour tissue was outside but adherent to the bony wall of the canal, but did not appear to extend into the bone to any appreciable depth. No abnormal deposits were noticed in the spines or laminae as these were cut through in exposing the cord.

The spinal arachnoid and the cord showed no macroscopic abnormality apart from compression.

Microscopically - Extradural tumour tissue showed a uniform, very cellular picture of close-packed cells with little or no stroma apart from the scanty amount around the rather thin walled blood vessels. The cells had a strong resemblance to plasma cells; an abundant cytoplasm deeply basophil and with, in many cases, a lighter staining, sometimes eosinophil area beside the nucleus. The nuclei were often eccentric, often with clumped cytoplasm, but sometimes oval or kidney shaped, with a more open chromatin meshwork. The single large nucleus is much less in evidence than usual. There was also a variety in size and the presence of 2 or 3 nuclei was frequent.

Bone Marrow - Solid greyish yellow, firm tissue like that of the vertebral canal replaced the marrow of the middle of the shaft of the right femur. The dense bone was not encroached upon.

The middle of the shaft of the right tibia contained fat.

Microscopically/

Microscopically - The block taken from the femur was entirely plasmacytomatous tissue like that described above. No haemopoietic cells were seen (Fig. 25).

The lymph-glands throughout the body were normal. Microscopically they showed a sinus histiocytic reaction and a little myeloid metaplasia in the medullary cords; plasma cells were not infrequent also, but there was no definite foci of myeloma cells.

Spleen was slightly enlarged. On section it was uniformly pale red in colour and much softened in consistence. The Malpighian corpuscles could not be seen.

Microscopically - In the block taken there was a great degree of myeloid metaplasia. Both sinuses and pulp were infiltrated with haemopoietic cells; among these haemocyto blasts and primitive erythroblasts predominated, but normoblasts were also numerous. Eosinophil myelocytes and polymorphs were not infrequent, but very few neutrophils were seen. Single or small groups of myeloma cells were not infrequent, but there was no large mass of myeloma tissue. (Fig. 26)

Liver - Normal size, with a smooth surface. On section the colour was pale yellowish brown, and unduly soft in consistence. The lobulation was indistinct, and there was no naked-eye evidence of infiltration of the liver tissue.

Microscopically - No large masses of myeloma were seen. The sinusoids, however, were filled everywhere with cells apparently of two origins. Some - haemocyto blasts and erythroblasts of various degrees of maturity - indicated myeloid metaplasia; but in addition there were numerous cells, single and in small groups, which were identical with myeloma cells. The portal tracts showed a little myeloid metaplasia, containing numerous eosinophil myelocytes and myelocytes. The liver cells showed slight fatty change.

Kidneys were both enlarged, pale, and had a smooth subcapsular surface. The striate vessels were congested and on section there was general pallor.

Microscopically - Frequent small foci of myeloid metaplasia. No deposits of myeloma cells. There was oedema of the stroma. Occasional tubules were distended and blocked by homogeneous eosinophil hyaline casts round which occasional giant-cell like bodies had formed.

Pancreas - A single strand of myeloma infiltration was seen.

Stomach/



Stomach & Heart showed a few subepithelial and subendocardial haemorrhages respectively.

No other abnormalities were found in the other organs, relevant to the condition.

Comment - No tumour found by X-ray.

Myeloma of plasma cell type.

Myeloid metaplasia very marked in spleen, liver and kidneys.

Deposits of myeloma cells in bones, extradural space, liver, spleen and pancreas.

Myeloma cells in the liver and spleen sinuses but not detected in the blood film.

Pain, loss of weight and anaemia.

## CASES OF PLASMACYTOMA PROVED BY BIOPSIES

### Case 9

George F.            Aet 86.            Retired Farmer.

Admitted - 19.6.35.    Discharged - 29.1.36.

Complaint - Swelling in the gum.

Abstract of Case - In January he thought he cut his gum with his lower teeth and awoke to find his mouth filled with blood. Since then the swelling has steadily grown at the site. It is not painful except when he touches anything with it.

Examination - Situated on the upper gum and projecting down from it, just to the left of the mid-line, is a fleshy looking mass  $\frac{1}{2}$ " in all dimensions. The lower surface is abraded by a tooth below and is bleeding. The mass is firm but not hard and is tender. The first left premolar which lies alongside it is loose. There is a similar but smaller swelling with an intact surface at the posterior end of the right upper gum.

Routine examination of the rest of the body showed nothing relevant.

On Admission - The X-ray report merely mentioned alveolar erosion of the right side of the upper jaw, and so a biopsy specimen was taken. This showed a typical plasma cell myeloma with characteristic component cells - eccentric nuclei, paranuclear clear zone, amphophilic cytoplasm, mitotic figures and many cells with 2 and 3 nuclei and prominent single nucleolus. There were areas of necrosis and much haemorrhage. (Fig. 33).

By 11.11.35 the right eye was protruding markedly and hanging like a bag on the upper cheek. It had been blind for  $1\frac{1}{2}$  years. There is no pain.

On examination a lump situated in the upper outer quadrant of the orbit grew from the orbital process of the frontal bone. The eye itself was not involved.

At this time also the upper end of the right ulna was swollen and irregular.

Between November 1935 and January 1936 the skeleton was X-rayed and, apart from the previous report, the only finding was a rounded, translucent area with slightly sclerotic margins just above the orbital/

orbital region of the skull. There was extensive osteoarthritis. The comment made was that the diagnosis of myeloma could not be verified radiologically, though the description seems like one. Later the right ulna was X-rayed and the appearances were reported as being like a giant cell tumour.

Comment - Plasma cell myeloma.  
Not recognised by X-ray.  
Older subject than usual.  
No pain or loss of weight.

### Case 10

Mrs Janet R, Aet 54.

Admitted - 5.3.36. Died - 18.3.36

Complaint - Abdominal pain for 9 weeks.

Abstract of Case - The abdominal pain bore no relation to meals and was worse at night and after taking exercise. It was dull in character and situated in the region of the gall bladder, but most severe when the patient straightens herself. The pain radiates to the back, but there is no history of biliary colic.

On Examination there was pain at the costal margin of both sides.

Spine - Kyphosis in the upper thoracic region.

Skull - A lump was found just above the right ear and a portion of this was later taken for biopsy.

<u>Blood</u> - R.B.C.	2.06 M.	Polymorphs	62%
W.B.C.	5,600	Lymphocytes	34%
Hb.	33%.	Eosinophiles	1%
C.I.	.8	Basophiles	.5%
		Transitionals	2.5%

Blood Calcium 10.0 mgm.%.

X-ray - There was erosion of the 5th dorsal vertebra and collapse of the 8th.

Skull - Numerous areas of bony change were seen of varying size, like secondary deposits.

Pelvis - Similarly, numerous metastatic deposits were seen, particularly on the left side.

Radiologically/



Radiologically the condition was considered one of carcinomatosis. (Figs. 41-43).

A biopsy from the lump above the right ear showed a plasma cell myeloma with no definite nucleolus.

Comment - Plasma cell myeloma.  
Pain related to the abdomen, and anaemia.

### Case 11

David B. Aet 69.

Admitted - 19.4.37. Discharged - 11.6.37.

Complaint - Pain in the breast bone.

Abstract of Case - Two months ago the patient began to complain of pain radiating from the top of his breast bone to behind the left ear. Shortly afterwards a swelling appeared at the top of the breast bone which at first grew quickly and then came to a standstill. Latterly a pain began to shoot down the left arm. Apart from this, he has been well, though lately he had been troubled with bronchitis.

Examination - Well built and healthy looking. There is a dome-shaped swelling  $2\frac{1}{2}$  inches in diameter replacing the manubrium sterni. Superficially it is soft and fluctuant, but the overlying skin is healthy.

It was not long, however, before the skin ulcerated and a discharge flowed.

There were no glands palpable and systematic examination of the body showed no detectable abnormality.

Two years later he complained of lumbar pain and died at home on 25.3.39. The initial local lesion improved greatly with X-ray therapy.

A Biopsy was taken and the tumour cells were typically those of a plasma cell myeloma, complete with eccentric nucleus, clear area, nucleolus prominent and clumped chromatin. A Foot stain for reticulin shows that very little of that substance had been formed. The cells are in sheets (Fig. 34). Wasserman Reaction was negative.

X-ray showed a broadening of the manubrium with irregular destruction of the cortex anteriorly. There were numerous rounded areas of decalcification. The diagnosis was given as lying between chondroma and chondrosarcoma. This opinion was, however, later reviewed in the light of the biopsy taken, and various parts/

parts of the skeleton were X-rayed and periodically re-examined. The changes in the sternum before X-ray therapy are shown and then during (7.6.37) and after treatment, 1.6.38 (Figs. 44-47). The tumour at first expanded and then gradually flattened.

By 18.5.38, 14 months after the initial symptoms, he complained of pain in the back and X-rays showed rarefaction of the lumbar spine and then a fortnight later, 1.6.38, collapse of the 1st dorsal vertebra was found, with herniation of the nucleus pulposus into the under aspect of the body. In the pelvis there was sclerosis of the right half along the border of the true pelvis, the acetabulum and the right os pubis. There was also sclerosis of the Sacrum in the region of the right sacro-iliac joint. (Fig. 48).

His condition gradually deteriorated and he died on 25.3.39, just over 2 years after the first symptom.

No myelomata were found in the skull or ribs.

Comment - Plasma cell type of myeloma.  
Sclerosis in the Pelvic Bones.  
Pain and loss of weight.

## Case 12

Mrs M. Aet 65.

Admitted - 26.7.34. Died - 1.3.37.

Complaint - Pain in both flanks.

Abstract of Case - For 2 years prior to admission the patient had pain in both flanks almost up to the ribs. It was constant for long periods, though never actually severe. No paraesthesia.

At the end of February 1933 she felt something give way in the back - no audible crack. A week later excruciating pain in the left lower abdomen, stabbing in type, and each attack lasting several minutes. This disappeared in 10 days. In June 1933 she consulted a chiropractor whose treatment was considerable pressure on the lumbar region. During the course she lost power of her legs, commencing with weakness of the knees. After the 12th dose she gave up this treatment, as the pain was severe, and in August she retired to a nursing home to be on a fracture bed for 2½ months.

In/

In February 1934 she was sufficiently improved to get up. Progress continued until 8th April, when within 24 hours she lost the power to stand erect. This followed on a little pain referred to the 9th and 10th vertebrae. Return to bed relieved the pain but weakness and loss of sensation gradually spread up both legs. She became incontinent of urine and constipated.

On Examination - The 10th thoracic spine was prominent.

Motor functions - Spastic paralysis of the leg muscles.

Sensory functions - Complete loss of all functions of cutaneous sensation below 12th thoracic segment, above which there is a zone of hyperaesthesia extending 2 segments above.

Babinski's sign in both feet.

X-rays at this time (17.7.34) showed a collapse anteriorly of the 10th thoracic vertebra, and considerable generalised decalcification in vertebrae and ribs. There was also some osteoarthritic lipping. At the lower border of the 10th thoracic vertebra a shadow extended well back into the vertebral canal (Figs. 49 & 50).

The skull and upper cervical vertebrae were normal.

A laminectomy was done and the patient improved enormously. No albuminuria yet recorded although tests were carried out, and no opinion of the pathological condition expressed.

By 9.5.35, about 2 years and 10 months after initial symptoms, there was a definite deterioration and lumbar puncture revealed a complete subarachnoid block; the previous laminectomy was extended. Now a tumour of bone was found and a biopsy specimen taken.

Sections of the biopsy showed the typical picture of the plasma cell myeloma with mitoses, haemorrhage and some necrosis. (Fig. 35).

X-ray therapy was started on 26.7.35. After the second laminectomy there was improvement, very gradual, over months. On 10.1.36 X-ray showed now that the 9th thoracic vertebra was collapsing in addition to the previously collapsed 10th, but that there was some recalcification of the affected vertebrae (Figs. 51 & 52).

By 30.9.36 she was up and about again, walking erect, but with some hyperaesthesia posteriorly between pelvis and scapulae. Kyphosis, if any, was/



was obscured. Rotation of the trunk passively caused no pain.

However, by 14.12.36 she had pain in the right shoulder and down the back of the right arm, and discomfort on the left side acromian region. Three days previously she heard a crack when using her arms to get out of bed and it was painful round both sterno-clavicular joints and tender to touch. The lower half of the body was still improving and on 4.1.37 she was X-rayed again.

At this time in the left shoulder there were multiple foci in the acromian process, scapula and head of humerus, but no foci in the ribs. Angulation  $2\frac{1}{2}$  inches below the head of the humerus was found - a sort of greenstick pathological fracture. (Fig. 53).

The right shoulder showed similar appearances, but the disease was less advanced in the humerus. No foci in the ribs.

The skull - Widespread foci in the calvarium. (Fig. 54).

The spine - The collapsed 9th and 10th vertebrae showed satisfactory calcification and the condition quiescent (Fig. 55).

Now for the first time Bence Jones protein was found in the urine.

Two months later on 1.3.37, i.e. over 4½ years after first symptoms, she died. No autopsy.

Comment - The disease appeared to have started in the 10th thoracic vertebra as a solitary plasmacytoma, and spread from there.  
The illness is unusually long.  
Bence Jones protein in the urine.  
Pain and loss of weight.

### Case 13

Robert G. Aet 65.

Admitted 9.3.38.

Abstract of Case - This patient first noticed a swelling in the sternal region in April 1937. It gradually increased in size. When examined there was found an irregular rounded swelling projecting from the upper part of the sternum and measuring 11 x 15 cm. His general health was poor.

Before admission on 26.2.38 a piece of tissue was taken from the sternum and the report of plasmacytoma issued. The section showed masses of myeloma cells of the typical plasma cell type, complete with its oval shape, eccentric, round nucleus with single nucleolus and clear area in abundant amphophilic cytoplasm, and, as is usually found, numerous/

numerous mitotic figures. (Fig. 36).

He improved a little with X-ray treatment till 5.8.38, when a plasmacytoma of the upper end of the right femur was reported by the radiologist. (Fig. 56).

When last seen on 15.5.40 he was reported to be well and the bone tumours had responded satisfactorily to treatment. He had put on 2 stone, 9 lbs. since treatment started.

Comment - Plasma cell myeloma.  
Clinical report very incomplete.

#### Case 14

John B.            Aet 28.            Lino-operator.

Admitted 4.10.38.    Discharged - 19.11.38.

Complaint - Swelling of right side of brow for  
2 years.  
Pain in the trunk and limbs for 2 years.  
Swellings on the bones of the chest for  
6 months.

Abstract of Case - Healthy until July 2 years ago, when a swelling about the size of a hen's egg developed on the right side of his brow as a result of bumping his head there. In August he noticed a pain localised to 3" in diameter across the front of the chest. The jaw was also tender and an attempt was made by his doctor to aspirate the swelling on the brow. It was eventually excised (December 1936) but 2 months later the swelling returned at a lower level, obstructing his vision. In March 1937 swellings noted in the lower back and by May 1937 he had pain in the legs, the left in particular causing him to limp, and he felt very weak. He was given X-ray therapy for 6 weeks to the head and back and ribs. He did not improve and the pains were now all over the skeleton. The appetite was failing and he grew weaker. Latterly the gums have bled readily.

Previously, at the age of 7, he cut his forehead badly.

On Examination - Below the scar in the right lateral forehead there is an irregular tumour mass which has elevated the right eyebrow and extends down into the right eye, displacing the eyeball downwards and resulting in diplopia. The tumour has a maximum diameter of 11.5 x 5 cm., is soft and does not feel fixed. There are four tumours overlying the ribs, the first in right lower ribs posteriorly/

posteriorly measuring 5 cm. in diameter; the second over the left lower ribs 4 cm. in diameter; the third over the lower ribs on right anteriorly 3 cm. across; and the fourth deep to the left nipple 3 cm. in diameter. All are mobile and soft. There is a smaller swelling 1 cm. across overlying the apex of the occipital bone and there is a depression in the upper part of the left mastoid region.

Blood R.B.C. 2.75 M. W.B.C. 11,000.

5.10.38 Wasserman Anticomplementary serum.  
Kahn Negative.

6.10.38 Differential count  
Polymorphs 75%  
Eosinophiles 1%  
Large lymphocytes 10%  
Small lymphocytes 9%  
Mononuclears 5%

2.11.38 Hb. 50%. R.B.C. 2.48 M.  
W.B.C. 6,200. C.I. 1.0.  
Retics. 1%.

Film - Red cells hypochromic and micro-  
cytic. No primitive cells.

Differential count  
Polymorphs 41%  
Large lymphocytes 15%  
Small lymphocytes 23%  
Monocytes 11%  
Eosinophiles 8%  
Basophiles 2%

Blood Sedimentation Rate 150 mm./hour.

#### Biochemist's Report

6.10.38 -	CO <sub>2</sub> Comb. Power	57 vol.%. 12.10.38	51 vol.%
12.10.38	Phosphorus	3.3 mgm.%	-
	Phosphatase	90 "	-
	Urea N.	11 "	- 12 mgm.%
	Magnesium	1.0 "	-
	Creatinine	1.0 "	- 1.8 "
	Albumen	2.0 gr.%	- 3.13 gr.%
	Globulin	10.08 "	- 10.63 "
	Calcium	10.4 mgm.%	-
	Cholesterol	180 "	- 167 mgm.%

Urinary System - No Bence Jones protein found but a trace of albumen was always present and blood and granular casts were found.

Blood Pressure 150/100.

NO/



No other relevant findings in routine examination of the other systems.

3.11.38 - Sternal Puncture - Occasional plasma cells seen but no significant increase. The marrow was more or less normal, apart from a moderate increase in eosinophil myelocytes. Puncture of the nodule in the upper sternum was a failure.

Biopsy, 4.12.36 - The section from the forehead shows a highly cellular characteristic plasma cell type of myeloma, with eccentric nucleus, nucleolus, amphophilic cytoplasm and paranuclear clear area. (Fig 37).

X-ray Reports (Figs. 57-60).

Skull - Several areas of bone destruction in the frontal region and a single area in the occipital region; also a smaller one in the parietal region.

Chest - Several areas of rib destruction with large tumours projecting into the chest.

Pelvis - Bone destruction in ischia, ilia and left pubic bone.

Vertebral Column - Collapse of the 10th dorsal and 3rd and 4th lumbar vertebrae. As there was some improvement with X-ray therapy the diagnosis of Schuller-Christian disease was made, but later that of plasmacytoma was reinstated.

The condition of the patient became worse and worse, and at the time of discharge on 19.11.38 it was reckoned that only a few weeks of life at the most remained.

Comment - Plasma cell myeloma.

Doubtful relationship to trauma.

Increase of phosphates and globulin with inversion of A:G ratio.

Increased blood sedimentation rate.

Younger age than usual.

Pain, loss of weight and anaemia.

### Case 15

Mrs Isabella M. Aet 58.

Admitted - 16.8.38. Died - March 1940.

Complaint - Pain between the shoulders and weakness.

Abstract of Case - In 1934 a dermoid cyst of the right ovary had been removed and at the same time she became rather crippled with rheumatoid arthritis, though this disease had been present for some 17 years. In July 1938 she noticed a swelling in her right leg to be followed 6 weeks later by "cramp" in the same leg, and when the bed pan was being removed she felt a crack in that leg and a shooting pain. The upper end/

end of the femur had broken. There had been "some thickening of the muscles" for some years previously. The femur mended in 6 months though she was unable to walk, and by April of 1939 the right arm broke while it was being lifted for massage "with the noise of a hundred cracks". A few weeks later she felt a constriction feeling of the chest and a loss of sensation down the inner wall of the arm, and there was pain across the shoulders and down the spine.

Almost exactly a year before the right leg broke she had fallen on the left hip; no serious injury.

Examination - There was a firm, hard and not tender, large swelling in the upper arm unattached to the skin, and no alteration of temperature over it. The arm is very oedematous. No signs of rheumatoid arthritis in the hands. No loss of sensation. The right leg had healed but with angulation of 150°. Palpation over the bones did not increase the patient's discomfort.

#### Blood Examination

##### 15.11.38 Differential Count

Neutrophiles	61.7%
Basophiles	0.6%
Eosinophiles	2.2%
Large lymphocytes	8 %
Small lymphocytes	24.1%

##### 23.11.39 Blood Chemistry

<u>Analysis</u>	<u>Result</u>
Cholesterol	111 mgm.%
Sugar	112 mgm.%
CO <sub>2</sub> Comb. Power	67 vols.%
Uric Acid	3.3 mgm.%
Phosphorus	2.5 mgm.%
Creatinine	1.0 mgm.%
Albumen	3.0 gm.%
Globulin	2.75 gm.%
Fibrinogen	0.30 gm.%
N.P.N.	36 mgm.%
Blood chloride (as NaCl)	448 mgm.%
Phosphatase	30
Calcium	9.0 mgm.%
24.11.39	
Urea	14 mgm.%

Blood Sedimentation rate 27 mm./hour.

Biopsy/

## Biopsy Reports

On 19.11.38 a biopsy was taken from the broken femur and the section showed a richly cellular typical plasma cell myeloma with cells packed closely together and batches of 20 or so at a time surrounded by reticulin. There were a few mitoses and the shape of the cells were often polygonal due to the close packing. (Fig. 38).

19.11.39 - Sternal Puncture - The needle entered very easily opposite the 3rd costal cartilage in the midline, and a large quantity of red gelatinous material was extracted. Plasma cells did not exceed an average of 18% on several counts. (Fig. 39-40a).

### Differential Marrow Count

Myeloblasts	4%	Lymphocytes	22%
Young forms	13%	Haemocytoblasts	3%
Stab cells	16%	Normoblasts	11%
Premyelocytes	13%	Plasma cells	18%

The plasma cells reacted well to the Unna Pappenheim stain and were peroxidase negative (Fig. 40a).

It was not until November 1939 that Bence Jones protein was found in the urine, and then in moderate quantities.

Routine examination of the other systems showed nothing relevant.

## X-ray Findings

15.12.38 - Extensive area of destruction involving junction of middle and upper thirds of shaft of right femur. The tumour is eroded into soft tissues so that the cortex is completely destroyed on the lateral side. The only new bone formation seems to be related to the fracture. No evidence of bone being produced by the tumour. There are several small rarefied areas in the femoral shaft at some distance from the site of the main involvement. The right tibia also shows small areas of involvement and there are numerous radio translucent areas in the skull. No metastases in the ribs or spine. Osteoarthritis of both hip joints.

8.9.39 - Right humerus: Destruction of the greater part of the shaft with very marked involvement of the middle third. In this area there is a complete defect.

Pelvis: The right pubic bone is eroded and the pelvic bones in general are rarefied.

The first 3 photographs of the femur show the monthly progress of callus formation from the initial fracture and the last photograph shows the femur at the time the arm broke. (Figs. 61-67).

Comment/



Comment - Plasma cell myeloma.  
 Phosphatase normal in spite of the  
 extensive lesions.  
 Total proteins the low side of normal.  
 Blood sedimentation rate moderately  
 increased.  
 Pain, loss of weight, and anaemia.

### Case 16

Mrs Mary B. Aet 60.

Admitted - 10.10.38. Discharged - 20.7.39.

Complaint - Pain in back and joints.

Abstract of Case - In 1936 the patient had pain in  
 and a swelling over the inner border of the right  
 clavicle, also pain down the right arm. This was  
 said to follow an electric shock she received. In  
 March 1938 she had pain in the back. She had  
 rheumatics for 10 years and now the joints were  
 stiffening. It was at first thought clinically  
 that the gall bladder was at fault, and while being  
 X-rayed for gall bladder function the lesion in the  
 ribs was found.

Examination - Good colour. No obvious loss of  
 weight. No abnormality found in the other bones -  
 skull smooth. Joint movement normal.

12.10.38 - X-ray report: Skull - Multiple  
 defects due to decalcification spread throughout  
 vault. (Figs. 73-75).

The whole of the spine and many of the ribs,  
 both scapulae, clavicles and humeri showed a  
 similar appearance. The sternum was poorly defined  
 due to calcification. The pelvis had similar  
 defects in both ilia, both pubes and both ischia.  
 Both femora, tibiae and fibulae were affected in the  
 same way.

The diagnosis of multiple myelomatosis or  
 possibly a parathyroid condition was made. (Figs. 74, 76-  
 Clinically no primary tumour was located. 80).

14.10.38 - Bence Jones protein in the urine -  
 strong positive.

Blood - 14.10.38  
 R.B.C. 3.99.M. Hb. 76%. C.I. .96.  
 M.C.V. 92. M.C.H.C. 25.

Differential/

Differential Count

Polymorphs	54.0%	Nest cells	2.0%
Lymphocytes	34.0%	Monocytes	8.0%
Eosinophiles	2.0%		

Coagulation time (inverted tube) 4 mins.  
Clot retraction normal.

25.10.38 - Biochemistry.

Blood Urea	60 mgm.%	Phosphorus	5.3 mgm.%
Uric Acid	4.6 mgm.%	Total Proteins	7.92%
Calcium	8.8 mgm.%	A:G ratio	normal.
		Phosphatase	normal.

Blood sedimentation rate 10 mm. at 1 hour.

17.11.38 - Sternal Puncture - Bone marrow smears show a uniform picture of typical plasma cells found in myelomata. There is an occasional neutrophil myelocyte and polymorph. (Fig. 68).

Blood Film - Differential Count -

Polymorphs	37.5%	Monocytes	3.5%
Lymphocytes	59.0%	No other types	found.

21.7.39 - A cyst appeared in the left side of the frontal bone and an X-ray of the skeleton showed further advance in the patchy decalcification and the right clavicle had fractured.

22.7.39 - Urea clearance Test 18.85%.

There was no improvement and the patient was discharged.

Comment - Plasmacytoma.

Very extensive skeletal involvement and yet no particular change in the Biochemistry findings.

Renal impairment.

Pain and anaemia.

Case 17

Robert F. Aet 56. Gas producer.

Admitted - 3.8.39. Died - 31.1.40.

Complaint - Pain in the back, right hip and above both eyes.

Abstract of Case - In May 1939 he fell on his right hip. It was painful and at the same time he felt pain in the lowest part of the back. The back pain lasted 4 weeks, off and on, movement of the spine bringing it on; the hip pain was less intense.

tense. He was confined to bed. Six weeks after the accident he tried to work again but after 5 days retired to bed.

A week after the accident he felt a pain over the right eyebrow, starting at the back of the neck and ascending behind the ear. It was dull and aching and his eyelid swelled up so that he could not open it. When he was able to do so, in 3 weeks, he had double vision. In September, 13 weeks after the accident, a corresponding pain was felt over the left eye, similar in character. The eyelid did not swell. According to his daughter ptosis was seen in the right eye some time before symptoms appeared. He received X-ray treatment and lying in a plaster jacket eased him.

On Examination - The 3rd nerve supply to the upper lid was still at least partially preserved, while the fibres to the extrinsic ocular muscles, both from the 3rd, 4th and 6th nerves, seemed to be completely out of action. There was slight depression of the ophthalmic division of the 5th. The right eye movement was good. Pupil reflexes active, but shape of pupils not quite regular.

Pain on percussing immediately above right zygomatic arch. No other skull tenderness.

Pain on palpating 6th dorsal and 2nd lumbar spines. The left 8th rib was tender in the anterior axillary line. Arteriosclerotic arteries were easily felt, and were seen in the fundi oculi, but no other lesion present.

He was gradually losing weight. No other relevant finding.

4.8.39 - C.S.F. Total protein 50 gm.%  
Sugar 68 mgm.%  
Chlorides (NaCl) 670 mgm.%

Wasserman reaction negative, but by 13.11.39 the serum was anticomplementary; poor clot retraction.

Blood sedimentation rate 7.8.39 - 127 mm./hr.

9.8.39 - 128 mm./hr.

Blood pressure 118/80 on an average with very little variation.

#### Blood Counts

<u>Date</u>	<u>R.B.C.</u>	<u>W.B.C.</u>	<u>Hb.</u>	<u>C.I.</u>	<u>Platelets</u>
4.8.39		6,800	72%		
9.8.39		6,000			
22.8.39	4.25 M.	8,200	82%	.96	
3.11.39	3.75 M.	5,000	86%	1.14	260,000
20.11.39	4.12 M.	4,600	86%	1.04	
30.11.39	4.05 M.	4,200	84%	1.03	

Differential/



Differential Counts

	<u>Poly-</u> <u>morphs</u>	<u>Lympho-</u> <u>cytes</u>	<u>Eosino-</u> <u>philes</u>	<u>Mono-</u> <u>cytes</u>	<u>Baso-</u> <u>philes</u>
9.8.39	60%	32%	4%	3%	1%
22.8.39	62%	31%	3%	4%	-
3.11.39	60%	29%	3%	8%	-
13.11.39	77%	15%	-	8%	-
20.11.39	69%	24%	3%	4%	-
30.11.39	57%	36%	1%	6%	-

All films showed some rouleaux formation.

Urine - Albumin was frequently found in the urine in traces, but Bence Jones protein only found on 5 occasions throughout his stay in hospital. Urea clearance 34.2%.

Biochemistry

	<u>9.8.39</u>	<u>6.11.39</u>	<u>24.11.39</u>
Phosphorus	4.0 mgm.%	3.9 mgm.%	-
Calcium	9.2 "	9.4 "	-
Phosphatase	71	60	-
Creatinine	-	-	1.3 mgm.%
Uric Acid	-	4.0 "	-
Cholesterol	-	-	115 "
Chlorides (NaCl)	-	520	"
Albumin	-	2.83 G.%	-
Globulin	-	7.25 "	-
Fibrinogen	-	0.73 "	-
N.P.N.	-	44 mgm.%	-
CO <sub>2</sub> Comb. Power	-	68 vols.%	-
Urea N.	-	21 mgm.%	-

Sternal Punctures - 11.8.39: In the midline opposite to 4th cartilage the needle went in easily and myeloma cells of the plasma cell type were present - 65%. The other marrow cells were in normal proportions..

7.11.39: Opposite the 3rd cartilage in the midline, a large quantity of thick red fluid tissue extracted. Myeloma cells were again much in evidence, to the extent of about 47%; other oxidase cells were 39%, normoblasts 8.5%, lymphocytes 5.5%. From this there was no doubt of the diagnosis of plasma cell myeloma. (Figs. 69-72).

17.11.39 - The skeleton was X-rayed. Pelvis, spine, both humeri and both femora show changes very typical of multiple myeloma. The ribs are rarefied but detail is obscured by lung markings. Large areas of rarefaction are seen at the lower end of the right femur, in the pubo-ischial ramus on the left side, in the 4th-rib on the left side and in the 9th rib on the right side. The skull is extremely interesting as there appear to be no changes in the vault. There is destruction of the apex of/

of the right petrous temporal, the dorsum sellae and an area in the left lower frontal region. First lumbar vertebra has a compressed fracture with altered texture of bone which is not typical of myelomatosis. (Figs. 88-98).

Comment - Plasma cell myeloma.

Increase of phosphatase and globulin and inversion of A:G ratio.

Nothing in the blood film beyond some rouleaux formation.

Blood sedimentation rate much increased.

Some renal impairment; Bence Jones protein.

Pain, loss of weight and mild anaemia.

Case 18

Charles E. Aet 50. Labourer.

Admitted - 11.3.37. Discharged - 12.2.40.

Complaint - Pain in the back and down the right side for 6 months.

Abstract of Case - His lumbago has been accompanied by a cough and the combination of the two caused him to go to bed. Though he ate well he was steadily losing weight. His chest condition was that of chronic bronchitis, but in his upper lumbar region there was a well marked gibbus. The part was tender to touch and rotation.

An X-ray at this time showed destruction of the 2nd lumbar vertebra and a confident diagnosis of benign giant cell tumour was made.

By 24.9.37 a pain in the right hip was troublesome, but he began deep X-ray therapy to the spine.

Meanwhile a swelling in the right iliac bone appeared and biopsy was done on 3.5.38 after X-rays showed a large cyst-like appearance on the upper part of the right ilium (2" x 3") as well as the collapsed 2nd lumbar vertebra. This lump was invading the bone extensively but not projecting into the soft tissues. It was very vascular, soft and greyish. It was reported as being an undifferentiated sarcoma which it quite clearly was not. The tissue on section was very vascular and cellular, the cells being those of a typical plasma cell myeloma with eccentric nucleus, central nucleolus, paranuclear clear area and amphophilic cytoplasm. (Fig 99). On 8.11.37 further X-ray examination showed multiple rounded areas of rarefaction throughout the skull, including the jaw, and myeloma was suggested. The gibbus was also beginning to heal.

No/

No primary tumour was ever located and apart from the chronic bronchitis nothing else of importance was recorded. (Figs. 101-103).

The bronchitis disappeared and his general condition improved until 12.7.39 when he was unable to walk because of pain in the right hip and leg, and there was a zone of hyperaesthesia extending from the level of the xyphisternum to the inguinal ligament on the right side, and on the back it extended to the middle of the thigh. The bronchitis was now worse than before.

On 10.8.39 he had an abscess situated over the old biopsy scar and directly connected with the ilium and extending over the iliac muscle. No tubercle bacilli found in it, but large numbers of pus cells with no pyogenic bacteria.

The weight was gradually decreasing. The B.P. varied between 80-110 systolic and fairly regularly 50 diastolic. The Wasserman reaction was always negative. By 3.1.40 he was very miserable again and the bronchitis was as bad as ever.

More detailed examinations were made and now he had tenderness over the 4th, 5th and 6th ribs in the axilla, the lower thoracic and upper lumbar spines, the right femur and the left humerus. Chest examination revealed much the same condition. Kidney function test by the Urea concentration Test gave a maximum figure of 3.0 and a minimum of 0.95. Between 14.1.40 and 13.2.40 attempts on 19 occasions were made to find Bence Jones protein but it was only found once in small quantities.

#### Blood Counts

<u>Date</u>	<u>R.B.C.</u>	<u>W.B.C.</u>	<u>Hb.</u>	<u>C.I.</u>
4.1.40	3.18 M.	7,800	62%	.97
10.1.40	2.98 M.	9,000	62%	1.04
17.1.40	2.52 M.	8,200	65%	1.2
22.1.40	2.68 M.	6,800	68%	1.2
31.1.40	2.15 M.	10,600	61%	1.4
2.2.40	-	7,800	75%	-
6.2.40	2.91 M.	6,600	62%	1.07

11.1.40 - Sternal Puncture (Fig.100) The bone was easily punctured in the midline opposite the 3rd cartilage. A moderate amount of red soft material was removed.

#### Differential Count

Myeloblasts	2%	Myelocytes	10%
Neutrophiles	35%	Normoblasts	9%
Stab cells	26%	Eosinophiles	2%
Lymphocytes	10%	Myeloma cells	6%

Blood/



Blood sedimentation rate on 10, 11 and 21.1.40 was 136, 136, 140.

### Blood Chemistry

#### Analysis

#### Result

	<u>4.1.40</u>	<u>15.1.40</u>	<u>22.1.40</u>	<u>30.1.40</u>
Albumen	1.53gm%	-	-	1.98 G%
Globulin	5.12gm%	-	-	7.83 G%
Fibrinogen	2.12gm%	-	1.05gm%	0.28 G%
Urea N.	18 mgm%	12 mgm%	-	23 mgm%
CO <sub>2</sub> Comb.				
Power	59 vols%	-	-	54 vols%
Uric Acid	3.2mgm%	-	-	2.7mgm%
Blood				
Chlorides				
(as NaCl)	470 mgm%	-	-	460 mgm%
Calcium	8.5mgm%	-	-	12.0mgm%
Phosphorus	3.4mgm%	4.1mgm%	-	4.3mgm%
Cholesterol	90 mgm%	-	-	100 mgm%
Phosphatase	-	48	-	81
N.P.M.	-	-	36 mgm%	48 mgm%
Creatinine	-	-	1.2mgm%	2.1mgm%
Sugar	-	-	-	98 mgm%

The patient was discharged with no improvement in the bronchitis but otherwise comfortable. Prognosis bad.

Comment - Plasma cell myeloma.  
 Sternal puncture not so positive as usual.  
 Renal impairment.  
 Phosphatase and globulin increased with inversion of A:G ratio.  
 Blood sedimentation rate much increased.  
 Bence Jones protein only found once.  
 Pain, Loss of weight, Anaemia.

### Case 19

John W.            Aet 42.            Married.            Printer.

Admitted - 8.3.40.    Discharged - 28.3.40.

Abstract of Case - When crossing the floor of his room, a stick on which he was leaning slipped and he fell heavily on the floor. There was immediate severe pain felt in the left hip which was worse on movement, and he was unable to walk. He had been in hospital four months ago for sciatica and was receiving X-ray therapy, and again eighteen months ago for the same trouble and treated by diathermy. Since the sciatica started he had been crippled, but his general health was good and the weight steady.  
 Examination/

Examination - The patient is a well nourished man and in considerable pain. There is an extra-capsular fracture of the left femoral neck. The left foot lies fully externally rotated and the leg is shortened by one inch. The left hip is full and there is pain on moving the hip joint.

Rectal examination - negative.

Routine examination of the various systems revealed no abnormality.

No other bony tumours or tenderness was found and in particular the sternum appeared to be normal in all respects.

#### Peripheral Blood Examination

R.B.C.	3.04 M.	Polymorphs	79%
W.B.C.	7,400	Lymphocytes	10%
Hb.	60%	Monocytes	9%
Retics.	5.4%	Eosinophiles	2%
Platelets	288,000	Basophiles	0%

Red cells do not show rouleaux formation.

17.3.40 - Bence Jones protein found in 24 hours specimen of urine in small amount, also on 26.3.40.

19.3.40 - Sternal Puncture was made in the midline at the junction of the 4th cartilage. The bone was soft and a large amount of marrow was sucked out. On examining the marrow smear it was obvious that a myeloma nodule had been hit, as nearly every cell was a myeloma cell with its eccentric nucleus, outstanding nucleolus, clear area and granular cytoplasm. Chromatin clumping is not seen (Figs. 104-5). Peroxidase reaction negative (Fig. 106). Unna Pappenheim stain strongly positive (Fig. 107). Urine albumen 4 G./litre.

Urine examination - Van Slyke Clearance Test - normal range.

Blood sedimentation rate 75 mm./hr.

Blood Wasserman negative.

19.3.40 -

Biochemistry/

Biochemistry

<u>Analysis</u>	<u>Result</u>	<u>Method</u>
Albumen	2.58 gm.%	Myers & Wardell.
Globulin	3.85 gm.%	" " "
Fibrinogen	0.45 gm.%	" " "
Inorganic Phosphorus	4.8 mgm.%	Briggs.
Phosphatase	103 mgm.%	"
CO <sub>2</sub> Comb. Power	68 vols.%	Van Slyke.
Iron	66 mgm.%	Wong.
Urea N.	20 mgm.%	Urease
Total fatty acids	147 mgm.%	Stewart & Hendry.
Lactic acid	12.5 mgm.%	von Tusek & Charnars.
Blood Chlorides (as NaCl)	444 mgm.%	Van Slyke.
Sugar	96 mgm.%	Hagedon & Lense.
Cholesterol	110 mgm.%	Myers.
Uric Acid	3.4 mgm.%	Benedict.
Creatinine	2.10 mgm.%	Folin.
Calcium	9 mgm.%	Kranmer & Tisdall
Sodium	327 mgm.%	Uranium Zinc Acetate.
Potassium	26 mgm.%	Platinum chloride
Magnesium	2.8 mgm.%	Denis.

X-ray shows a fracture of the femur neck through a large cyst like cavity growing from within, diagnosed as a myeloma. (Fig. 110).

Comment - Plasma cell type of myeloma.  
Increased magnesium, phosphatase and globulin with inversion of A:G ratio.  
Increased Blood Sedimentation rate.  
Pain and anaemia.

Case 20

William B.            Aet 56.            Paper mill worker.

Admitted - 29.5.40.    Discharged - 18.8.40.

Complaint - Pain in back from neck to right leg, 6 months.

Abstract of Case - Patient's symptoms started 6 months ago with sciatic like pain in the right leg which extended soon to the back and back of neck. The leg was numbed, stiff, and became thinner. The appetite was fairly good but 2 weeks prior to admission there was much loss of weight. He was inclined to sweat.

On examination there was marked loss of sensation below the right knee, and the leg was atrophied; a sciatic type of pain could be elicited. No bony tenderness; no albuminuria.

No other clinical abnormality was noticed.  
Kidney/



Kidney function normal.

The condition was not recognised at the beginning and various examinations proved negative. C.S.F. normal. Tuberculosis was considered possible.

30.6.40 - Wasserman negative. B.P. 120/70.

### Blood

30.6.40 - R.B.C. 3.94 M. W.B.C. 4,200. Hb 68%  
19.7.40 2.45 M. 3,000 55%

### Blood Chemistry

	<u>11.7.40</u>	<u>26.7.40</u>
Albumen	2.8 G.%	2.56 G.%
Globulin	3.98 G.%	4.12 G.%
Fibrinogen	-	0.25 G.%
Phosphorus	4.0 mgm.%	2.8 mgm.%
Sugar	100 mgm.%	105 mgm.%
Uric Acid	5.0 mgm.%	-
Urea N.	24 mgm.%	27 mgm.%
CO <sub>2</sub> Comb. Power	68 vols.%	45 vols.%
Iron	66 mgm.%	75 mgm.%
Calcium	12.7 mgm.%	10.0 mgm.%
Magnesium	1.3 mgm.%	-
Cholesterol	122 mgm.%	100 mgm.%
Phosphatase	36	67
Chlorides as NaCl	698 mgm.%	-

31.5.40 - X-ray: Area of bone destruction in the right ilium adjacent to the sacro-iliac joint, due either to osteolytic metastatic deposit or alternatively to a plasmacytoma. (Figs. 111 & 112).

Lungs - Pneumoconiosis with emphysema.

Further X-ray report on 25.6.40 added that there was an area of destruction at the left acetabulum and numerous small areas throughout the pelvis and upper ends of the femora.

Similar changes found in the skull.

Spine - Involvement of 6th dorsal vertebra.

Ribs - Destruction of left 10th near its neck and right 3rd.

The diagnosis of plasmacytoma passing on to the multiple stage was made.

1.7.40 - Sternal Puncture. Very few typical myeloma cells were seen, about 2%, otherwise the picture was normal and no diagnosis could be made by this method. (Fig. 108).

18.7.40 - Puncture made 1 inch further up the sternum than previously and this time quite a different picture was seen. Typical plasma myeloma cells/

cells were present 65%. (Fig. 109).

Bence Jones protein found in the urine.

The patient continued to lose weight, and was discharged 18.8.40.

Comment - The uncertainty of sternal puncture is shown though in the first sternal puncture the plasma cells were primitive.  
Diagnosis by X-ray.  
Plasma cell myeloma.  
Bence Jones protein.  
Increase of phosphatase and globulin with inversion of A:G ratio.  
Pain, loss of weight, anaemia.

### Case 21

#### CASE OF EXTRAMEDULLARY PLASMACYTOMA

John H.            Aet 63.            Porter.

Admitted - 9.1.34.    Died - 5.2.34.

Complaint - Hoarseness and difficulty in swallowing for 2 weeks.

On Examination the left tonsil was very much enlarged, hard, comparatively mobile, and appeared malignant. There were no glands palpable. Because of the swallowing difficulty, oesophagoscopy was performed and a growth extending for 4 cm. was found 23 cm. from the teeth. A biopsy of this was taken but no evidence of malignancy was seen. The mucous glands were hypertrophied. At the same time the left tonsil was excised and on section it was seen that the lymphoid tissue was replaced by a diffuse proliferation of cells resembling plasma cells and identical with myeloma cells of that type, complete with amphophilic cytoplasm, clear area, eccentric round nucleus and prominent nucleolus. No mitotic figures seen. A diagnosis of extra-medullary plasma cell myeloma was made. (Fig. 113).

The blood Wasserman was negative.

There is no further information available; no positive relevant finding is recorded.

The patient died on 5.2.34. Cause unknown.

Comment - Plasma cell tumour, apparently localised to the tonsil, the so-called extra-medullary type.

CASES OF PLASMACYTOMA  
SHOWING LEUKAEMIC MANIFESTATIONS

Case 22

Helen B.            Aet 37.            Tailoress.

Admitted - 18.9.30.    Died - 27.4.31.

Complaint - Pain in arms, legs and chest, <sup>like</sup> growing pains, for 6 weeks.

Abstract of History - The pains complained of were not localised to the joints but were also in the muscles. She was becoming more easily tired. Appetite good.

On Examination - Pale and listless. The chest pain is made worse with coughing. There is marked cardiac decompensation and signs of pleurisy were found. B.P. 120/45. Double aortic murmur. Wasserman reaction negative.

<u>Blood</u> -	<u>21.9.30</u>	<u>2.11.30</u>	<u>6.11.30</u>
R.B.C.	2.92 M.	1.74 M.	-
W.B.C.	58,000	8,200	18,800
Hb	44%	31%	-
C.I.	0.76	0.91	-

The anaemia progressed and the W.B.C. fell to 8,200, to rise four days later to 18,800, as revealed above, but no longer a picture of lymphatic leukaemia as previously reckoned.

Differential Counts

	<u>21.9.30</u>	<u>25.9.30</u>	<u>6.11.30</u>	<u>20.11.30</u>
Polymorphs	17	30.0	52.5	37.0
Myelocytes	7	5.3	9.5	9.0
Myeloblasts	-	.7	0	0
Small Lymphocytes	46	59.3	29.0	40.0
Large Lymphocytes	29	-	-	13.0
Monocytes	-	3.3	6.0	-
Eosinophiles	1.0	1.0	3.0	1.0

Spleen, liver and glands not enlarged. No tumour felt. Before being sent to a convalescent home the W.B.C. was 7,000 and with 52.5% polymorphs and 9.5% myelocytes the picture was more like an infective leukocytosis. The pleurisy healed and signs of pericarditis were found. On 20.11.30 the picture was again one of lymphatic leukaemia as shown above.

Some weeks at a convalescent home did not improve/



improve her, and a swelling appeared on the forehead which was painful, and pain again occurred in legs & arms, and the speech was indistinct.

Blood Count - 22.4.31

R.B.C. 3,400,000. W.B.C. 14,000. Hb 56%. C.I. 0.82.

X-ray diagnosis was osteitis fibrosa and a tumour was recognised in the frontal bone.

All this time the cardiac condition only mildly improved, and emaciation rapidly increased and movement became more and more painful.

On palpating some of the ribs a cracking sensation was experienced but no fractures or alteration in any of the bones of the skeleton, apart from the skull, was found.

Crepitations were heard at the lung bases, but apart from this, routine examination of the other systems revealed no abnormality. The urine contained no albumen, but the excretion of calcium was much increased.

23.4.31 - Blood Phosphorus 4.9 mgm.%  
Serum Calcium 15.9 mgm.%  
Phosphatase 70

A further X-ray report of the skull states the presence of numerous round cyst spaces in the bone, perfectly punched out; the largest was in the frontal bone and the other spaces were smaller.

The description is typical of myeloma, but the diagnosis of osteitis fibrosa was again given, the definite increase in serum calcium supporting the diagnosis.

Four days before death, the following blood examination was made -

R.B.C. 2,240,000. W.B.C. 21,200. Hb 48%. C.I. 1.06.  
Reticulocytes  $\frac{1}{2}$ %. Normoblasts 7.5%.

Differential Count

Myelocytes	3.0%
Band cells	8.0%
Polymorphs	28.0%
Lymphocytes	57.5%
Monocytes	2.5%
Mast cells	1.0%

At/



At autopsy the diagnosis of myelomatosis was established and on reviewing the opinion of the blood picture it was thought that the blood cells termed lymphocytes were myeloblasts. They could just as easily have been plasma cells.

In the treatment prescribed Calcium Lactate Gr. XV 2 hourly was given.

### Abstract of Autopsy

The body was that of a normally developed but emaciated female. The subcutaneous fat was orange-yellow in colour.

### Osseous System

Skull - In the vault there were numbers of small, sharply defined areas of erosion of the bone in which deposits of pale red tissue were seen. These areas varied in size and age from 3 mm. in diameter to 2 cm. This latter was in the frontal bone and the inner plate was perforated. The edges were sharply defined and had a punched out appearance. On the surface of the inner plate of the skull was a fine white deposit of calcium. Numerous deposits of myeloid-like tissue, with destruction of bone were found in the occipital bone, particularly on the left side. On the right half was an irregular osteophytic formation.

Sternum - The manubrium was almost completely hollowed out and filled with excess of myeloid tissue.

The Right Scapula was markedly affected in a similar way and the acromion was easily broken while removing the bone.

All the large bones were affected and the medullary centres were considerably increased in size and filled with a marrow pale greyish red in colour, and scattered through the tissue were many dark red patches. Some of these had invaded the compact bone and had formed little cyst-like spaces.

Microscopically - A section from the femur was taken as a typical example. The entire marrow is infiltrated with myelomatous tissue, all the cells of which are similar in type, being a large nucleus centrally placed in an amphophilic cytoplasm almost devoid of any clear area. The nuclear chromatin is typically clumped along the nuclear membrane and a nucleolus is prominent. There are many binucleated cells in which the chromatin is dense. (Fig. 114).

Brain and its coverings - The outer surface of the dura was of a chalky white appearance and it was thickened/

thickened. No actual calcification was found in this deposit of calcium. The inner surface of the dura was studded with numerous haemorrhagic spots.

The pia arachnoid, brain and pituitary were pale but otherwise normal.

Microscopically - Dura mater: Several deposits of calcium are seen in a thickened membrane. Small aggregations of plasma cells are present.

#### Lymphatic System

These are enlarged mainly in the region of the thyroid. Some of the mesenteric glands are calcified.

Microscopically - The peripheral sinus is almost filled with cells, many of which are myeloma cells. Histiocytes and lymphocytes are also numerous. The architecture of the gland is altered; germinal centres are lost and myeloma cells are seen in large quantities in the centre of the gland in different stages and with 1 to 4 nuclei. The colour of the cytoplasm varies considerably from pale blue to pale pink (Fig. 115).

Liver - Enlarged, pale and coarsely mottled, giving a dense haemosiderin reaction.

Microscopically - The general picture is similar to that of myelogenous leukaemia with the majority of sinusoids filled with nucleated cells - the portal tracts being almost normal under high power. These cells are identical with the myeloma cells described above which are of the plasma cell type and it is extremely probable that they are identical with the cells seen in the peripheral blood films, which leads to the supposition that the condition of plasma cell leukaemia was present (Figs. 116 & 117).

Spleen weighed 290 g. and was enlarged, moderately firm, and red in colour. On section there were numerous minute dark red patches and the Malpighian bodies were ill defined. The haemosiderin reaction was positive.

Microscopically - The reticulin is not increased but the sinusoids are packed with myeloma cells and some few lymphocytes. There is no tumour and the Malpighian bodies are difficult to locate as myeloma cells infiltrate them just as easily (Fig. 118).

Pancreas - Average size and of firm consistence, surrounded by white areas like fat necrosis.

Microscopically - The parenchyma and islet tissue is normal but there are bands of myelomatous infiltration coursing over the section.

Kidneys - Average size. The capsule stripped easily/



easily leaving a smooth, congested surface. On section the cortex-medulla ratio was normal but evenly scattered throughout the parenchyma were small pin-point white dots. Pelvis normal.

Microscopically - The cortex is congested. There is a heavy infiltration of myeloma cells identical with those described above, diffusely spread throughout the section. The convoluted tubules show cloudy swelling and other tubules are frequently atrophied, especially when completely surrounded by myeloma cells. The connective tissue is mildly increased and the glomeruli are practically undamaged, the only observation worthy of note being the marked congestion. The blood vessels are normal. Casts are scarce and stain either blue or orange with Azan. Several patches of calcification are seen in some of the tubules apparently starting in the basement membrane and breaking into the lumen. It is somewhat like the picture seen in Vitaminosis D (Fig. 119).

Summary - Plasma cell myeloma.  
 Plasma cell leukaemia.  
 Infiltration of liver, spleen, kidney, pancreas, lymph glands and dura mater.  
 Clinically and radiologically diagnosed as osteitis fibrosa cystica.  
 Calcium deposits in dura mater and kidney.  
 Increase in calcium and phosphatase.  
 Pain, loss of weight and anaemia.

### Case 23

Charles S. Aet 49.

Admitted - 24.6.38. Died - 1.9.39.

Complaint - Squeezing pain in the right chest for 6 weeks.

Abstract of History - Eight weeks before admission he was struck in the right chest by a crowbar. The part was painful to touch and a week later he had a writhing pain between the shoulder blades on breathing. This shifted about sometimes being in the right chest, sometimes the left, and occasionally in the back, but never in any other part of the body. There was no coughing of blood and no swelling at the site of injury, but he was very much paler than he used to be. There were haemorrhages into the sclerotics of the left eye.

Examination - Tenderness on pressure over the 7th and 8th dorsal spines, also an area round the right nipple/

nipple, the lowerhalf of the sternum, in the right axilla and the second left rib. Liver and spleen normal. Haemorrhages in both retinae.

X-rays - 25.6.38: No fractures in ribs, sternum nor spine. 4.7.38: Generalised osteoporosis - no cysts demonstrable, but later cystic formation was seen in the ribs.

Wasserman reaction negative. Serum calcium 9.8 mgm.%. The anaemia progressed, abnormal cells appeared in the blood, pneumonia developed and death occurred on 1.9.39.

#### Blood Examination

	<u>30.6.38</u>	<u>12.7.38</u>	<u>29.7.38</u>	<u>8.8.38</u>	<u>25.8.38</u>
R.B.C.	2.62 M	2.34 M	-	1.77 M	1.72 M
W.B.C.	11,600	9,200	-	7,800	9,600
Hb	50%	40%	38%	35%	35%
C.I.	0.95	0.85	-	0.99	1.01
Retics.	1%	1%	-	-	-

#### Differential Counts

	<u>30.6.38</u>	<u>25.8.38</u>
Polymorphs	20.0%	22 %
Eosinophiles	1.0%	2 %
Basophiles	0 %	0 %
Monocytes	1.5%	1 %
Lymphocytes	32.5%	35 %
Metamyelocytes	13.5%	1 %
Türch cells	31.5%	39 %
Normoblasts	1 per 200 W.B.C.	0 %

The Türch cells are shown in Fig. 120.

#### Abstract of Autopsy

The body was that of a thin, pale, moderately well nourished man of average height. The subcutaneous fat was deep yellow and numerous nodules were seen on the ribs.

Osseous System - The bones were very thin and could easily be cut with a pair of scissors, while fractures were present on the right side in each of the ribs from the 2nd to the 10th and on the left side in the 1st to the 4th and 8th and 9th ribs. On the left side there was also a mass at the junction of the 1st rib with the manubrium sterni. The manubrium was extensively involved and the central part of the bone was filled with a greyish white/

white tumour tissue. The involvement was most marked in the region of the junction of the manubrium with the body of the bone.

Small deposits were found in the lumbar spine and the upper part of the shaft of the right femur.

Microscopically - Bone Marrow: Almost entirely replaced by tumour tissue consisting of masses of mononuclear round cells of varied size, 10 - 12 $\mu$  in diameter. The cytoplasm is granular and basophil. The nuclei are large and often eccentrically placed. The chromatin mesh is fine and there is generally a well defined, small nucleolus. There are a small number of cells with dense nuclei. Unna Pappenheim reaction is not typical. Rarely were other marrow cells seen. These neoplastic cells were identical with those seen in the blood stream called Tüsch cells.

Lungs showed pneumonia.

Liver and spleen were not enlarged but microscopically in the spleen there was an increase in reticulum cells and in cells resembling the tumour cells.

Kidney - Occasional intratubular calcium deposits. finding

No other relevant/is recorded.

Summary - Plasma cell myeloma showing leukaemic manifestations.

#### CASE OF PLASMA CELL LEUKAEMIA WITHOUT MYELOMA

##### Case 24

Mrs Millicent W.      Aet 61.      Nurse.

Admitted - 30.11.39.      Died - 18.1.40.

Complaint - Pain in the neck, breathlessness,  
loss of weight.

Abstract of Case - In the past month she has lost 1½ stones in weight. Pain in the neck for 5 days.

In appearance she is cyanosed and dyspnoeic. The occipital, cervical, axillary and inguinal glands are enlarged. The spleen is enlarged.

Urine - albumen +. Bence Jones protein not found.

Wasserman reaction negative.

Blood/



Blood Counts

	<u>R.B.C.</u>	<u>W.B.C.</u>	<u>Hb</u>	<u>C.I.</u>
10.12.39	4.5 M	16,000	65	.72
11.12.39	-	22,000	-	-
12.12.39	-	20,000	78%	-
13.12.39	3.6 M	19,000	78%	1.08
14.12.39	3.58 M	10,600	80%	1.1
16.12.39	-	7,800	85%	-
18.12.39	-	5,500	85%	-
19.12.39	4.1 M	10,800	85%	1.01
21.12.39	-	6,000	-	-
24.12.39	3.69 M	5,800	85%	1.15

Differential Counts

	<u>12.12.39</u>	<u>18.12.39</u>
Polymorphs	39%	61%
Lymphocytes	9%	13%
Monocytes	11%	17%
Eosinophiles	2%	1%
Türch cells	39%	8%

Blood Film - Figs. 121-124,

13.12.39 - Sternal Puncture: Parts of the marrow are quite normal in cellular content but there are parts where there is an excess of cells of haemocytoblast appearance and there are numerous clumps of slightly smaller basophil cells showing transitions to plasma cells and again another large group of cells which are undoubtedly plasma cells and identical with those cells found in a plasma cell myeloma. (Fig. 125).

Biopsy of Lymph Gland - Sections from cervical lymph node show destruction of the normal architecture. It is densely infiltrated with plasma cells and there is also a considerable infiltration with eosinophiles.

Both in marrow and lymph node the infiltrating mononuclears were peroxidase negative.

The picture suggests a plasma cell leukaemia. (Fig. 126).

X-rays only showed enlarged hilar glands. No bony changes.

Abstract of Autopsy

The body was that of a reasonably nourished, middle-aged woman of average build. There was a sparse, fine purpuric eruption and small haemorrhagic moist papules scattered all over the body.

Lymph Nodes - Cervical, hilar, para-aortic, mesenteric and inguinal nodes were enlarged up to the size of a walnut, and on section were of pale pink-grey colour and of soft consistence.

Microscopically they all showed the same picture as the biopsy gland.

Osseous/

Osseous System - There was no sign of tumour formation but the upper two-thirds of the left femur, half the sternum, a rib and a wedge from the bodies of lumbar vertebrae 3, 4 and 5 were removed. Sternum and vertebrae showed the cancellous bone occupied by red marrow of normal appearance, and there was no evidence of focal abnormal infiltration.

Shaft of femur also showed a homogeneous dark red marrow.

Microscopically - Bone Marrow: The cellular marrow is not uniformly leukaemic; myeloblasts, erythrocytes and neutrophile granular cells are everywhere present, although all in considerably reduced proportions. Eosinophiles are increased. Haemocytoblasts are moderately increased in number. The chief change is the presence of two types of cell, firstly typical plasma cells and secondly cells with larger nuclei of more open chromatin work and without the clear area of the plasma cell. In many cases it is difficult to distinguish these cells from miniature erythroblasts; comparison with the biopsy sternal puncture smears, however, shows that most of them are not erythroblasts and that they are identical with the Tüsch cells seen in the blood film. In every case they were peroxidase negative.

Liver was normal in size and gave a negative peroxidase reaction.

Microscopically the portal tracts show considerable infiltration with the two abnormal cell types seen in the marrow and eosinophiles are also conspicuous. The abnormal cell types are also seen in the sinusoids but there is no real infiltration. The distribution therefore is that characteristic of lymphatic leukaemia. (Fig. 127).

Spleen was enlarged; weight 1250 g. The capsule was smooth. On section the spleen was pale creamy red and studded with paler dots, suggesting enlarged Malpighian bodies. There were occasional larger nodules (3 - 4 mm.) of yellow grey colour. It was much softened and the iron reaction was faint positive.

Microscopically - The pulp was heavily infiltrated with cells similar to those in the lymph nodes and other organs. (Fig. 128).

Kidneys and Pancreas also showed small leukaemic infiltrations.

Small Intestine - There were many small petechiae in the ileum.

The other organs showed no findings of importance.

### Comment

This leukaemia is certainly not myeloid. The eosinophil element in the tissue infiltrations is interesting and unexplained, but the eosinophiles are largely/

largely polymorph and there is no neutrophil infiltration. The cells which are really leukaemic are all oxidase negative. Monocytic leukaemia appears unlikely; the cells are small for monoblasts, and there is no tendency to the indentation of the nucleus so characteristic of monocytes. A lymphatic leukaemia remains possible, but the striking numbers of plasma cells in the infiltrations is very suggestive of a plasma cell leukaemia or a lymphatic leukaemia with plasma cell differentiation. The occurrence of many Tüch cells in the blood, as seen here, has been noted in cases of plasma cell leukaemia. The case differs from a plasma cell myelomatosis with blood involvement in the absence of focal infiltrations of the bones.

Summary - Plasma cell leukaemia.

No focal deposits, therefore not a myelomatous condition.

Pain, loss of weight, anaemia.

CASES OF MYELOMA WITH MYELOBLASTIC TYPE OF CELL

Case 25

David R.            Aet 40.            Unemployed miner.

Onset of symptoms March 1929.    Died 31.12.31.

Abstract of Case Record - In March 1929 he felt pain in the sternum and clavicles, and lumps appeared in these bones. Deep X-ray therapy improved him while in hospital in July 1930. He was fairly well until April 1931 when pain again affected him. In December 1930 he noticed a tender swelling above the left buttock. This swelling remained stationary but pain gradually returned to the chest and was so bad that he was readmitted to hospital in April 1931. At the end of September of that year he had numbness in his legs, and a week after the initial nervous symptoms there was paraplegia from the xyphisternum downwards. Towards the end of October swellings appeared at the back of the neck, ribs, skull and clavicles. He died on 31.12.31.

1.5.30 - A biopsy was taken from the outer end of the clavicle. The tissue examined showed a widespread infiltrating growth which was composed of round cells containing a large round nucleus with more than one prominent nucleolus, though only one could be seen at a given depth of focus, and so the photograph is deceptive (Fig. 129). The chromatin meshwork is thin/



thin and open. The cytoplasm is very scanty and basophilic and no clear area could possibly be contained in it. Morphologically they were identical with myeloblasts. A foot stain shows that a good deal of reticulum is being laid down, often pericellular (Fig. 130).

No clinical findings are available unfortunately.

#### X-ray Findings

Skull - Several clearly punched out areas in the vault are seen, of variable size, but all are circular (Fig. 139 & 140).

Right Shoulder - Clavicle and acromion show medullary translucency due to a tumour growing from within and causing thinning of the compact bone. The outer end of the clavicle is swollen and there is considerable rarefaction (Fig. 141).

Sternum - The normal appearance of the sternum is entirely altered. Egg-shell bone is seen and both anterior and posterior aspects are wavy. The entire bone is diseased (Fig. 142).

Thoracic Vertebrae - There was partial collapse of thoracic 8th.

Ribs - All show rarefaction and are probably myelomatous, but obvious changes are in the 5th, 9th, 10th and 11th on the right side and in 6th, 8th, 11th and 12th on the left. Spontaneous fractures have occurred for instance in the 5th and 9th on the right side (Fig. 143).

Pelvis - Both iliac bones show large tumours (Fig. 144).

Right forearm - The periosteum is thickened and the distal ends of the bones are rarefied (Fig. 145).

Autopsy specimens of the heads of both femurs, part of the sternum and the right clavicle show the gross destruction of bone from within. (Fig. 146-148).

#### Abstract of Autopsy

The body was normally developed but emaciated. Small tumour nodules of a bluish colour were present in the subcutaneous tissue over the thorax and abdominal wall.

A micro section of the subcutaneous tissue showed myelomatous tissue growing along the connective tissue framework, so that strands of it course over the field (Fig. 131).

Bone Marrow - The marrow of the shaft of the femur was hyperplastic and very dark red in colour and resembled tumour growth.

Microscopically - The section is divided into two types of tissue, one of abnormal marrow and the other/

other of new growth

In the marrow part there is a slight increase in the myeloid series but clusters of plasma cells are clearly seen at P. in Fig. 132.

By far the majority have an eccentric nucleus and amphophilic cytoplasm. The chromatin is "cartwheel" in distribution (Fig. 133). In the new growth part there are sheets of cells with but little supporting tissue or else the same type of cell with moderately thick supporting tissue bands forming compartments for groups of 10 - 20 cells. These latter cells are like myeloblasts and may contain so many as four nucleoli (Fig. 134). Sometimes there is a tendency for the nuclear chromatin to cluster round the nuclear membrane, but nothing to the same degree as in the typical "radkern" type. Scattered here and there are areas of necrosis where the cytoplasmic reaction is eosinophilic, and the nuclei assume ring or partial ring formations. These cells are identical with the biopsy cells but the nucleoli do not stand out so violently eosinophilic.

Skull - In the vault numerous small nodes of tumour growth were present. In one area, however, 3 cm. in diameter the tumour had disappeared and new bone had formed round the periphery and in the centre the bone was much thinned - probably a reaction to X-rays. There was a haemorrhagic node in the posterior fossa of the skull and one in the anterior fossa over the roof of the left orbit.

Brain was normal but the dura mater was sprinkled with small nodes of tumour (Fig. 135).

Microscopically this tumour was seen to cling to the under surface of the dura and there was haemorrhage at the periphery.

Thoracic Cage - Tumour growths were on the pleural surface of the 4th and 8th ribs on the left side and on the 4th, 5th and 9th ribs on the right side. Growths were also found in the sternum and acromial ends of both clavicles.

Pericardium - There was a tumour mass on the anterior surface of the parietal pericardium.

Lungs, heart, stomach, alimentary tract, liver, gall bladder, spleen and kidneys showed no tumour growth, though the spleen was twice its usual size, and on section the sinusoids were partly filled with myeloid metaplasia. There was no metaplasia in the kidney nor other relevant change, but a few myeloma cells were seen in the liver sinusoids.

Pancreas - Enlarged, firm in consistence and throughout the entire gland was seen infiltration of white homogeneous tissue resembling tumour growth. On section the parenchyma was freely infiltrated with myelomatous tissue sometimes in mass but more frequently evenly spread so that numerous individual acini were surrounded. The adjacent omental fat was also/

also infiltrated (Fig. 136).

The Suprarenals were both involved in tumour growth which had spread from perinephric neoplastic tissue on both sides.

A section of skeletal muscle shows the distribution of the myelomatous tissue and the wisps of muscle fibres through it (Fig. 137). The solid growth is identical with that previously described but the cellular infiltration of the invaded muscle is partially lymphocytic and partially plasmacytic of the classical inflammatory type - It is about half and half (Fig. 138).

Comment - The malignant cell is myeloblastic in type.

The excessive typical plasma cells in the bone marrow is perhaps reactive in origin and apparently not neoplastic yet. There is definite metastasis.

Myeloma cells are present in the sinusoids of spleen and liver; (no peripheral blood film was available).

The extensive growths throughout the skeleton.

The duration of  $2\frac{1}{2}$  years from initial symptoms.

## Case 26

Jean L. Aet 33.

Admitted - 23.5.26. Discharged - 19.6.26.

Complaint - Pain in the right leg.

Abstract of History - Sciatica in the right leg 20 years ago. This healed entirely until it returned 1 year ago, but this time had not responded to treatment and was most severe when she sat. The pain had a wider distribution than formerly, ranging from the crest of the ilium, down the back of the thigh, popliteal region and outside of the leg.

On Examination there was tenderness and thickening over anterior superior iliac spine and over the lower dorsal vertebrae.

Wasserman reaction negative.

A Biopsy was taken from the iliac spine. The material was greyish and had a sarcomatous appearance and was subperiosteal in position.

On section the tissue was composed of round cells with large nuclei containing at least two nucleoli/



nucleoli and at times tending to be kidney shaped. The cytoplasm was blue and spare and rarely could something suggesting a paranuclear clear area be seen. The cells were similar to myeloblasts and sprinkled amongst them were cells with clumped chromatin in their nuclei but no recognisable cytoplasm. The nuclei, however, were very similar to those seen in some plasma cell myelomata, but in this case were pyknotic myeloblasts (Fig. 149).

The radiologist reported numerous irregular areas of decalcification in the head of the right femur, right acetabulum and right ischium. No opinion was expressed. The photographs are not available.

There are no other clinical or laboratory findings reported.

She was discharged on 19.6.26, still having pain and knowing that nothing could be done for her.

Comment - Apparently myeloblastic myeloma, but no blood picture available.

#### DOUBTFUL CASES

##### Case 27

John C.                      Aet 17 years.                      Glazer and lead worker.

Admitted 11.3.26.

Abstract of Case - The patient had carious teeth and extraction was recommended. Shortly after a molar was removed a swelling appeared in its site and the next tooth ached. Eventually all the carious teeth were removed and he enjoyed good health. Eight weeks after the first extraction there was a swelling of the left thigh, which subsided leaving a lump in the middle, tender on pressure. Very soon after the right thigh swelled, especially behind the knee, and there was pain on extending the knee joint. The swelling increased and a week later lumps were present on the point of the chin and behind the left ear, to be followed closely by one on the back of the neck. No pain and no systemic disturbance. By the time he was in hospital 12 weeks after the teeth extractions there were scattered lumps over the chest, abdomen, axilla and back and a large lump on the anterior aspect of the lateral part of the middle of his/

his left leg, situated in the muscle. The right knee was semiflexed and a large brawny swelling in the popliteal space could be felt, non pulsatile, no fluctuation, and only slight pain on pressure. The joint itself was not involved. There was also an intramuscular lump in the anterior tibial muscles of the left leg - painless. The lumps on the chest and head were fixed to the bone.

### Blood

R.B.C. 4.5 M. W.B.C. 8,200.

### Differential Count

Polymorphs	73%
Basophiles (which included a number of myeloblasts, the percentage not stated)	.6%
Transitional cells	2.3%
Large mononuclears	.6%
Large lymphocytes	14.2%
Small lymphocytes	9.1%

A biopsy was made from a tumour behind the ear. It was attached to the bone and a dark red mass of material was removed.

On section the tissue is composed of closely packed cells nearly all of the same type, with a large nucleus, 2, 3, or 4 nucleoli and scarce cytoplasm, basophilic in reaction and containing no clear area. The chromatin of the nucleus is very open and the general appearance is that of a myeloblast. There is extensive mitoses. (Fig. 150).

Urine Examination - Albumen was found in fairly large quantities but the Bence Jones reaction was doubtful.

X-rays of the femora showed some elevation and thickening of the lateral aspects of shafts. No definite diagnosis was made. The photographs are not available.

The lymph glands were not enlarged nor was liver or spleen, and routine examination of the other systems was negative.

The tumours were increasing rapidly and ensuing in new places over night. He became more and more crippled/

crippled daily and his parents insisted on his re-  
turning home.

Comment - This case was considered one of myelomatosis, myeloblastic in type, but with consideration for the type of cell, the clinical picture, the blood picture and the age of the individual, it is much more likely to be a leukaemia with numerous skin nodules, i.e. leukaemia cutis, the blood picture showing an aleukaemic phase.

## Case 28

John E.            Aet 52.            Unemployed craneman.

Admitted - 19.12.31. Died 23.12.31.

Complaint - Pain in the side for 3 months.

Abstract of History - The patient was badly wounded in the war in the right hip and right foot. The right foot was amputated and the stump gave trouble for years. For the past few months he has been suffering from recurrent attacks of bronchitis and pleurisy and for 3 months he has had albuminuria.

Urinary System - Albumen .1%; a few hyaline casts; no blood.

In the examination of the other systems no relevant observation was made.

B.P. 140/80. Wasserman reaction negative.

Non-protein nitrogen 43 mgm.%; creatinine 3.5 mgm.%.  
 100

Clinically the condition was thought to be parenchymatous nephritis, death being due to uraemic coma or cerebral haemorrhage.

### Abstract of Autopsy

The body was that of a well developed, middle-aged male.

Kidneys were large and very pale. The capsule stripped readily leaving a smooth surface. On section both cortex and medulla were paler than normal and in general there was a mottled appearance, congested vessels showing up clearly. The appearances were suggestive of parenchymatous nephritis.

Microscopically/



Microscopically - Numerous casts were seen in the tubules, some staining yellow with Azan. The tubules showed general toxic change and there was a very mild diffuse increase in the connective tissue. In the cortex there was partial fibrosis of isolated nephrons and one or two glomeruli were congested and even free blood was present in the capsule. Mild intracapillary fibrosis was frequently seen. The condition was an early chronic parenchymatous nephritis. However, scattered irregularly about were aggregations of blood cells mainly white and in the majority of instances entirely white. They were not examples of myeloid metaplasia, but more like leukaemic infiltrations. No plasma cells were seen

Brain - No evidence of tumour or haemorrhage.

Bone Marrow was more active than usual but no definite pathological condition was observed.

Microscopically an intense leucoblastic reaction was seen and there were large numbers of cells with round nuclei and 1 to 3 nucleoli and ample cytoplasm, devoid of a clear area. They were a mixture of myeloblasts and early myelocytes. Eosinophilic metamyelocytes were numerous.

There was little hyperplasia of the red cell series.

This was considered a myeloma, myelocytic in type. (Fig. 151).

Growth on Rib - The cells are similar to those described in the bone marrow.

Routine examination of the other organs in the body showed nothing relevant.

Comment - Death from parenchymatous nephritis.

This was considered a case of myeloma, but it is much more likely to be a myeloid leukaemia showing infiltration in the kidney and a chloromatous condition of the rib.

Unfortunately sections of the liver are not available.

Though sufficient evidence for real criticism is lacking, this case appears to be more a myeloid leukaemia than a myeloma, but the features are mixed. It is much more likely to be a case of chloroma.

CASES/

CASES DIAGNOSED RADIOLOGICALLY AS

MYELOMA - NO VERIFICATION

Case 29

Mrs Sarah S.            Aet 58.            At home.

Admitted - 12.2.36.    Discharged - 11.3.36.

Complaint - Pain low down in the back.

Abstract of Case - "Rheumatism" for 4 months, starting in the right hip, soon to pass to the other hip and both thighs. The pain would radiate from the buttocks to the front and down each thigh, and made worse while stooping. A month ago - 8 months after the onset - the pain in fact became very severe and patient was confined to bed, unable to sit up.

Examination - Considerable pain on pressure over the spines of the lower three lumbar vertebrae - particularly the fourth. No other bone abnormality nor tenderness was found.

Urine - Albumen +. Bence Jones protein present.  
Blood calcium and phosphorus normal.

Routine examination revealed no abnormality in the other systems and no primary growth was found.

X-rays - Dorsal and lumbar spine show multiple areas of rarefaction. The 4th lumbar vertebra is collapsed. All the ribs show multiple radio translucent areas, as do also the skull, left humerus and femur, and the pelvis (Figs. 152-154).

The diagnosis of multiple myeloma was made.

Comment - X-ray diagnosis only. Appearances are typical and nearly every bone is involved.  
Severe pain.  
Bence Jones protein.

Case 30

James R.            Aet 57.

Admitted - 20.4.37.    Discharged 27.4.37.

Complaint - Pain in the left side.

Abstract of Case - The patient has had a dull ache in the left rib margin for 7 months (since October 1936). The left shoulder became stiff 2½ months ago and the right/

right shoulder followed 14 days later. Six weeks before admission the left shoulder improved but the right shoulder pain persisted. Pain in the lower abdomen radiating to the back started a week later, to be closely followed by a sudden acute pain in the back of the neck lasting 7 days. His appetite was good and apart from the pains he felt fit.

Examination - There was an oval lump one inch long in the centre of each clavicle and the left sternoclavicular joint was enlarged. The shoulder joint appeared normal. There was much tenderness on deep palpation over the 10th rib in the anterior axillary line. Pressure over the lumbar muscles on the level of the first lumbar vertebra was painful.

Routine examination of the various systems showed no abnormality.

#### X-ray Reports

Deposits typical of multiple myeloma were found in the skull, femora, humeri, scapulae, clavicles, ribs and vertebrae. Some of these are shown (Figs. 155-160).

Comment - X-ray diagnosis only. Appearances typical. Pain.

#### Case 31

Mrs Marjorie S. Aet 52. At home.

Admitted - 6.1.38. Died 18.2.38.

Complaint - Pains across the chest for 3 weeks.

Abstract of Case - The patient was fit until 6 months ago when she felt a tightness across the chest and was recommended to take it easy. Four months later pain came to the small of the back and five weeks after this the chest pain became severe and was constantly present, sometimes very acute and made worse on movement. On the day of admission she vomited blood stained fluid twice.

On Examination she looked thin and ill with a tinge of jaundice. Percussion over the sternum was painful. There was no enlargement of spleen, liver or lymph glands.

B.P. 178/108. Urine - negative. Wasserman reaction negative.

Blood - R.B.C. 5.22 M. W.B.C. 9,600.  
Hb. 99% (Haldane).

All/



All the other systems were examined but no abnormality found. Her condition became worse and worse and she died on 18.2.38.

X-rays - 3 weeks before death: Rarefaction and destruction of the lower part of the 2nd cervical vertebra - appearances which at first suggested a giant cell tumour but later photographs showed small areas of rarefaction in the left humerus and femur, and the sternum was osteoporotic and mildly expanded, though no definite lesion was found. (Fig. 161).

The diagnosis of multiple myeloma was made.

Comment - X-rays diagnosis only, but the appearances were characteristic.

Pain.

### Case 32

Mrs Jean N. Aet 67.

Admitted - 19.5.38. Died 16.11.38.

Abstract of Case - The patient complained of pain in the small of the back for about 8 months. She has not been able to walk since the pain began. It is continual and gnawing in character. She feels that "the bones in the back have softened and dropped".

X-rays showed widespread metastatic deposits involving the dorsal and lumbar spine, ribs, pelvis and upper part of the femora. The body of dorsal vertebra 6 has collapsed.

The diagnosis of multiple myeloma was made, the picture being considered typical. (Fig. 162 & 163).

Comment - X-ray diagnosis. Appearances typical. Severe pain.

### CASES DIAGNOSED INCORRECTLY AS MYELOMA

#### Case 33

Elizabeth B. Aet 56. At home.

Admitted - 5.5.35. Died 23.12.35.

Complaint - Pain in the stomach and back for 16 months.

Abstract of Case - For some years the patient had suffered from gastric discomfort and in 4 years had lost 5 stones in weight. General medical examination did not/

not reveal any carcinomatous condition though a thorough search was made.

X-ray examination revealed multiple areas of rarefaction in all the bones - skull, vertebral column, ribs, pelvis, clavicles, humeri and femora. It was noted that in the long bones these areas were connected with the medullary cavities and were apparently eroding the cortical bone from within and it was concluded that the condition was one of multiple myelomatosis. (Figs. 164-167).

Subsequently a biopsy of a rib was performed and the section showed a secondary adenocarcinoma; the primary growth was never found but it certainly was not a myeloma.

Urine - No Bence Jones protein.

Blood - Calcium 10.7 mgm.%  
Phosphorus 2.2 mgm.%

Comment - A case of adenocarcinomatosis of the skeleton, the bony destruction and appearance as shown by X-ray identical with myelomatosis.

#### Case 34

William S. Aet 37.

Admitted - 17.9.38. Died - 15.12.38.

Complaint - Severe headache.

Abstract of Case - When first seen the patient complained of headache and recent loss of weight for which on careful clinical examination no cause could be found, and his headache was considered functional. Two months later, however, he had bony swellings above both eyes and pain in the head, back and legs. The left eyeball protruded.

On Examination - No abnormal masses or tenderness was found apart from the skull and again clinical examination was of little help.

#### Blood

	<u>15.11.38</u>	<u>24.11.38</u>
R.B.C.	4.03 M.	3.25 M.
W.B.C.	18,400	13,800
Hb	67%	62%
C.I.	0.84	0.95
Retics.		1.8%

Blood film - R.B.C. hypochromic.  
Blood/

Blood Sedimentation rate 89 mm./hr.

Wasserman reaction negative.

Urine - Slight trace of albumen. Bence Jones protein negative.

### Biochemistry

Albumen	2.64 g.%	CO <sub>2</sub> Comb.Power	61 vols.%
Globulin	4.53 g.%	Urea N.	11 mgm.%
Calcium	105 mgm.%	Phosphatase	61
Magnesium	1.4 mgm.%	Cholesterol	160 mgm.%
Phosphorus	4.3 mgm.%	Creatinine	1.4 mgm.%

X-rays showed destruction of the 5th, 7th and 8th ribs on the left side, posteriorly, an area of destruction of the left clavicle and some destruction of the left scapula in the region of the glenoid; similar areas in the left olecranon process and in the anterior aspect of the lower end of the left humerus.

Skull - Numerous areas of destruction in the frontal region, especially the right side.

Pelvis - Areas of destruction in the right ilium close to the sacro-iliac joint and in the right pubo-ischial ramus. There are several areas of destruction in the upper ends of the femora.

Spine - Destruction of the bodies of the 9th dorsal and 1st lumbar vertebrae.

All the areas showed no sign of reaction and the appearances suggested myelomatosis. (Figs. 168-171).

Biopsy of a gland indicated a secondary carcinoma and autopsy proved the case to be one of carcinoma of the bronchus.

Comment - The similarity between this case of carcinomatosis of bone and some of the cases of myeloma is interesting. The biochemical findings are characteristic of myeloma - increased globulin and phosphatase and inversion of A:G ratio, and the X-ray pictures are very similar. The symptoms of bony pain, loss of weight and anaemia are also suggestive.

### Case 35

Mrs Mary L. Aet 55.

Admitted - 26.10.38.

Complaint - Pain in the legs.

Abstract/



Abstract of Case - Six months ago the patient developed pain in the legs, lower back, upper anterior part of the chest and the arms. The pains tended to flit and headaches were sporadic. There was loss of weight. The joints did not swell. The diagnosis was rheumatism but when in hospital a carcinoma of the right breast was found. The carcinomatous condition was rather hidden and in between the times when the rheumatism was diagnosed and her entry into hospital an X-ray report of a probable myelomatosis was given, to be changed when the breast condition became more obvious. The X-rays are shown as an example of the similarity between some cases of skeletal carcinomatosis and myelomatosis.

Photographs showed small irregular areas of decalcification in the skull, mandible, the whole length of the spine, both humeri, clavicles, scapulae, the ribs, pelvis, and both femora, and possibly a similar change in both tibiae. (Figs. 172-178).

Urine - Bence Jones protein absent.

Blood - R.B.C. 1,56 M. W.B.C. 8,450. Hb 27%.  
C.I. 0.86. Retics. 2.5%. M.C.H.C. 21.7.

#### Biochemistry

Serum Calcium	11.2 mgm.%	Albumen	4.25g.%
Phosphorus	4.7 mgm.%	Globulin	2.00g.%
Phosphatase - Much increased.		Urea	45.0mgm%
	Uric acid	3.3 mgm.%	
	B.S.R.	77 mm./hr.	

Comment - This case is shown purely because of the initial tentative diagnosis of myelomatosis by the radiologist before a primary lesion was found. It is also interesting to notice the high B.S.R. without an increase in the globulin figure.

## AETIOLOGY

### Age

Multiple myeloma is a disease of later life and Geschickter and Copeland find that 80% of all cases occur between the ages of 40 and 70 with a peak incidence at 55, a figure in agreement with other recorded statistics. Young adults are much less commonly afflicted, and only 15% of the cases occur in the age group 21 - 40. Reports of myeloma in children are not wanting but there is some doubt as to the authenticity of the diagnosis as many are made purely on X-ray finding and such an opinion must be held with reserve. Six cases have been proved by autopsy, though not all of these have microscopical reports, three are called myeloma, one myeloblastic myeloma, one myeloblastic plus erythroblastic myeloma and one plasmacytoma; this last occurring in a male infant of 16 months, the youngest on record - Hager, Roen and Paterson (1933).

The range of the cases in my series is from 28 to 86 years in those considered definitely to be myeloma, with an average age of 54 years. In only 3 instances was the age below 40 years.

### Sex

Men are more frequently affected than women in the proportion of over 2 to 1, it is stated; in my series the proportion was almost 3 to 1, including histologically/

histologically proven cases only.

### Occurrence

Reports come from all parts of the Continent, from the Americas, Australia and China, and indeed there is no reason to suppose that any race or colour of man in whatever stratum of society should be exempt.

### Incidence

Attempts at estimating the incidence have been rather unsatisfactory and widely divergent figures are quoted in the literature. Geschickter and Copeland base their figure on life insurance tables which record a percentage for sarcomata, and thus, in rather an illogical fashion, the proportion of myelomata in 400 sarcomata gives a percentage of 0.03 of all malignancies, i.e. 3 per 10,000.

In my experience six cases have been examined in twelve months in the Royal Infirmary, Edinburgh, and one outside. These were proved histologically. To be added to these are another probable three or four radiologically diagnosed in patients to whom I had no access. Colonel Harvey of the Royal College of Physicians Laboratory has very kindly allowed me to examine the slides from which he made the diagnosis of myeloma - biopsies, over the past 12 years. Fourteen cases of plasmacytoma were found in Edinburgh alone, apart from the material collected/



collected by me at the Royal Infirmary where, out of 40 cases claimed to be myeloma, 19 were plasmacytoma and 2 possibly myeloblastic myelomata. The remaining cases were myeloid sarcomata or giant cell tumours of bone where the term myeloma was loosely used. Add to these 4 diagnoses made solely by the radiologist which are included in my series but lack pathological proof. Some odd cases are added, the source of which is acknowledged elsewhere. From these Edinburgh figures alone myeloma cannot be considered an excessively rare disease.

It is true that a particularly diligent search has been made in the past year for myelomata and the result indicates that the disease has previously been missed and there has been lacking histological proof, but it may be ascertained from the figures quoted that myeloma is much more common than Geschickter and Copeland believe it to be.

Family history has on occasion been stressed as a possible cause; predecessors with cancer, pernicious anaemia, or a brother also with myeloma indicate chance findings and are not at all convincing. I have never been able to find a connection. There seems to be little evidence emerged from a study of family history.

Trauma is not an unnatural source of inquiry, but it would not be difficult to find some history of/

of accident, particularly as more than double the incidence is associated with the aggressive male, but when the disease has become manifest some slight injury may be the immediate means of revealing the neoplastic condition in the form of a pathological fracture. As a causation alone trauma probably has nothing to do with myeloma. Where it occurred in the cases in my series it was the means of revealing the preformed disease, as probably in all malignant diseases of bone.

Infection. There is also no real evidence for suspecting an infection of any kind as a causal agent unless possibly some virus as yet unknown - Furth (1933). Associations of syphilis, influenza, malaria, tuberculosis and many other diseases are entirely incidental as any one of them may attack the individual at one time in his life history.

Thus the aetiology of myeloma remains unknown like so many other malignant diseases.

## SYMPTOMATOLOGY

The chief symptoms and clinical characteristics in myeloma are pain, anaemia, loss of weight and bone deformity. In almost every case three of these signs are present and two of them always present. Fracture and clinical tumour formation are only very slightly less frequent and indeed all six symptoms are present in over 90% of the cases. Other signs may be found on clinical examination but are less frequent and some attention will be paid to them later; among them is the presence of Bence-Jones proteose in the urine.

### Pain

This is undoubtedly the commonest symptom and at some time throughout the course of the disease it is invariably present. Frequently it is the presenting symptom and, as is shown in some of the cases in my series, it is not unusual to have a patient complain of sciatica for a longer or shorter period before some other catastrophe, such as a pathological fracture, stimulates the clinician to enquire more thoroughly into his case and thus ultimately reach the correct diagnosis.

Rheumatism, including osteoarthritis, is another diagnosis made before the actual cause of the pain has made itself more clear.

At the onset, to describe the pain as "rheumatic" is not at all inaccurate, as very frequently/



frequently it is intermittent, made worse on movement, and wandering. Pain is most often associated with the lumbar and sacral regions, thus being one more to add to the varied pathology already involved in production of low back pain. It is perhaps this common situation for pain in both sexes of middle age which may dull some doctors' keenness for investigation, and a dissatisfied patient seeks relief from less reputable sources, even at the hands of a chiropractor, as in case 12 in my series, with disastrous results.

As the pain may at times be sciatic in type, to find other neuritic distributions would be quite in keeping with the pathological situation causing such symptoms, that is to say, disease of a vertebra being so advanced as to precipitate fracture, and girdle sensations and pains of small or widespread distribution are thus often present. They may be mild but clearly it is possible for the process to go to the extent of a paraplegia giving a picture not unlike a transverse myelitis. Cases No. 6, 12, and 25 show a picture like this.

Sharp attacks of pain may occur brought on by sudden movement, or a sustained muscular effort may be enough to fracture a bone. Such an accident may occur in a mine as in case No. 4, and probably lead to compensation claims. Numerous different ways of producing such a catastrophe are to be found in the literature, for example, the sudden halting/

halting of a train, running downstairs, being bounced about in a fast travelling bus, and so on.

When the accident does occur, the pain is very great indeed, taking hours or days to pass away, but eventually it will disappear and be absent for months or years until some reminders of the previous torture return in short sharp bursts which herald the last stages of increasing pain which remain in varying intensity until death.

Chest pains, including ribs and sternum, are next in frequency, but less common than the lumbar and sacral variety which, according to Geschickter and Copeland, are about 70% and the chest pains 20%, leaving 5% for distribution in the legs, arms and shoulders and 5% for the rest of the body.

My figures are rather different. The chest pains were nearly as common as the lumbo-sacral type and when the latter occurred pain in the leg frequently followed, often typically sciatic. Pain in some form was nearly always present, and where not mentioned it is probably due to lack of sufficient notes.

Thus the course of pain is erratic; it is characteristically at the beginning the rheumatic, sciatic, neuralgic, low back type, made worse on movement and frequently described by the patient as lumbago, suddenly and violently accentuated by a catastrophe such as vertebral collapse or other pathological fracture, when the pain is unbearable, followed by relief for months or years interrupted by/

by occasional twinges which slowly increase in frequency, leading up in a crescendo to continued agony and the last phase of prostration and death.

### The Blood

#### Anaemia

In the myeloma cases reported in which blood counts and other pertinent observations have been made, an anaemia is an extremely common, though not universal, finding, and blood pictures of all kinds have been demonstrated. These may be of primary or secondary anaemia, or polycythaemia, of leucopenia or leucaemia. So often the cases are not proved histologically and frequently the observations were made fairly early in the disease, but for a longer or shorter time before death and almost invariably terminally, anaemia is a usual finding, with a red cell count of about  $3\frac{1}{2}$  millions or less, and a low colour index.

In my own cases in which a blood count was done this observation is supported, the dissensions being in those in which counts were made some months before death, and the final picture is not known.

There is probably nothing very remarkable about this, as anaemia is a common observation in other cancerous conditions, but some explanation may be found in the knowledge that large parts of the bone marrow are frequently replaced by neoplastic tissue and the body may find this a serious loss to/



What is  
Primary  
anaemia?  
SD

to the extent that myeloid metaplasia can sometimes be demonstrated in liver, spleen and kidney. That some of the cases may show a primary anaemia is very hard to explain - possibly coincidental.

#### Differential Count

Usually little information is obtained from the differential count; some outstanding exceptions are dealt with under the section on plasma cell leucaemia. Türk cells are seen occasionally. Otherwise nondescript pictures are revealed, such as the presence of normoblasts, myeloblasts, myelocytes, an increase in the monocytes or eosinophils. It is well known that in any cancerous condition with metastases to the bone marrow, or in terminal pictures of pernicious anaemia, and other variable diseases in which the bone marrow may be primarily or secondarily affected, to find an odd array of primitive cells in the peripheral blood is not very exceptional, and though there are several cases published claiming unusual blood pictures, I do not consider them in any way characteristic of myeloma, nor are they helpful in the diagnosis, with the exception, I repeat, of the presence of the Türk cell, but not on that observation alone.

A leucocytosis is often mentioned, but as so many cases die of an intercurrent infection no further comment is necessary.

I would mention a paper by Vaughan (1936) concerning leuco-erythroblastic anaemia. In 18 cases of myeloma one such case of this form of anaemia was found. In this there appeared to be no relation between the degree of the anaemia and the extent of bone involvement which was quite extensive. In my series, case 22 is a possible case of leuco-erythroblastic anaemia, but this form of anaemia is no more indicative of myeloma than it is of any other carcinomatosis or terminal leucaemia where there is intense bone marrow irritation.

Definite anaemia was found in 13 of my cases of myeloma, that is to say, in all but one in which some blood examination was made. The one dissension is case 31, where an early radiological diagnosis was made.

#### Loss of Weight

As in other malignant conditions, this feature is to be expected. Attention is drawn to it merely because it may occur quite early in the disease and if associated with lumbar or any other bony pain, suspicion at once should be aroused and a full clinical examination begun. The loss of weight is not always progressive and in the intermissions the former weight may be regained and also after X-ray treatment; but when this form of treatment is completed and remissions start/

start again the loss of weight is frequently sudden and marked, and no improvement follows. In my series there is not usually any definite investigation into loss of weight, but the patient volunteers the information in 15, i.e. half, of the cases.

### Deformity

Although bony deformity associated with myeloma has been known for many years and even a cursory acquaintance with the disease process is a sufficient explanation in itself, too little attention is paid to this very important sign in the diagnosis of the disease. Radiologically it is of great importance. The most usual conditions which are confusing to the clinician are carcinomatosis, osteitis deformans, osteitis fibrosa cystica and osteomalacia. In myeloma 60% show thoracic deformity, according to Geschickter and Copeland. This is a fair estimation, when the examination is complete. The sternum is frequently the site of tumour or depression and always the ribs should be carefully palpated in their entire length, as the finding of at least one nodule and frequently more, is a commonplace. There is no particular site of election. The clavicle is considered to be nearly as common a situation as the ribs, but this is not borne out in/



in my series. In contrast with Geschickter and Copeland, I found that the extremities were quite often involved, in two-thirds of my cases, mainly the humerus and femur, and particularly the latter. Other bones of the extremities are comparatively rarely affected (See Table).

The skull, a favourite site for myeloma, only shows deformity clinically, in that protruding nodules may be palpated anywhere and we read of cases where the teeth begin to fall out, not unlike case No. 9, but there should be no difficulty in differentiating between this type of deformity and that of osteitis deformans. Generally the nodularity or the extent of the involvement cannot be accurately gauged clinically.

Also there is no bending of the extremities as in osteitis deformans and osteomalacia, and fractures may heal well leaving scarcely any deformity, with good treatment.

Lastly, the vertebral column, perhaps the most characteristic site of deformity; here scoliosis, kyphosis, flattening of the lumbar curve and the telescoping of one or more vertebral bodies are as common as the frequency of lumbar pain would indicate. A glance at Fig. 3 will demonstrate why this happens. In this photograph the nodules, as in Fig. 2, have coalesced and the bone structure weakened/

Table to show the distribution and possible extent of bone involvement in cases of myeloma. Much detail is lacking, either because a thorough autopsy has not been done or because clinical data is lacking. It is compiled with the help of X-ray photographs.

The bone involvement thus tabulated is then a minimum and in most cases probably a gross understatement.

Case	Skull	Vertebrae			Sternum	Ribs	Pelvic Bones				Humerus	Ulna	Scapula	Clavicle	Femur	Tibia	Fibula	
		Cerv.	Dors.	Lumb.			Sacr.	Il.	Isch.	Pubis								
1							+	+										
2			+															
3		+	+	+	+													
4	+		+	+	+	+									+			
5	+		+		+	+		+	+		+				+			
6			+	+	+	+												
7	+				+	+												
8				+	+										+			(No bone damage detected by X-ray.
9	+											+						(Probably diffuse infiltration in
10	+		+															all bones.
11			+		+													Sclerosis of pelvic bones.
12	+		+								+		+	+				
13					+										+			
14	+		+	+		+		+	+	+								
15	+				+					+	+				+	+	+	
16	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	
17	+		+	+	+	+		+	+	+	+				+			
18	+		+	+	+	+		+		+	+				+			
19					+										+			
20	+		+		+	+		+	+	+					+			
21																		Extra-osseous myeloma.
22	+				+	+					+	+	+		+			
23			+	+	+	+									+			
25	+		+		+	+		+					+	+	+			
26								+	+						+			
29	+		+	+		+		+		+	+				+			
30	+	+	+	+	+	+					+		+	+	+			
31		+			+						+				+			
32			+	+		+		+							+			



weakened, collapses.

As a result of vertebral collapse the patient changes his gait; he is more careful and deliberate; he tires easily; the abdomen protrudes and he throws his shoulders back; he walks on a wider base to keep his balance if, indeed, he is fortunate enough to be able to move about without neuralgic pain so severe as to confine him to bed.

The deformity may resemble tuberculosis of the spine clinically at a first impression, but the history of the illness, consideration of the age of the patient and the more localised condition should help to eliminate tuberculosis, which scarcely ever is a real difficulty in diagnosis. The collapse may be so marked as to cause the lower ribs to approximate to the iliac crest almost to the point of touching them.

The Table shows the distribution of bony involvement in my series of cases. It is certain that more bones were involved than the Table indicates.

### Fracture

A corollary to bone deformity is fracture due to the fragility of the bone resulting from the tumour which by nature erodes from within. Fracture is a common event in myeloma and in any given case may be multiple. Atkinson considers Geschickter and Copeland's figure of 62% of cases of myeloma showing fracture to be too high, but I think it is, if anything/



anything, an under estimate, because on autopsy one or more fractures not diagnosed in life may be revealed; particularly does this refer to the ribs. This figure is twice that estimated for fracture complicating metastatic carcinoma.

Fracture is frequently the first indication of the disease; a rib may break spontaneously, simulating acute pleurisy, and accidentally stubbing the toe against a leg of a chair may fracture the hip, and of course diverse histories on the same pattern are recorded.

The commonest site of fracture is the thoracic cage, particularly the ribs; much less frequently the clavicles and sternum. The extremities are more seldom affected, and then confined to the humerus and femur almost entirely.

United and ununited fractures are described, the latter being more prevalent in cases where X-ray therapy was not used, but with its help union is more usual and often within a normal period. Without X-rays most authors report that union is generally slow, when it does occur.

Fracture is a result of, not a cause of myeloma.

### Tumour

Among other possibilities tumour formation may be the presenting sign. The distribution of these tumours is characteristically multiple, though this is not by any means a necessary feature. Some attention/

attention will be paid to the existence of solitary myelomata in another section, and these are mainly associated with the extra-medullary plasmacytoma almost entirely localised to the pharyngeal and upper respiratory passages.

It is of course probable that one bone may be the seat of a myeloma rapidly increasing in size, and so attracting attention to the eclipse of any other tumour formation which probably could only be found at a detailed autopsy. Radiologically only one tumour may be found, but the radiologist is not infallible. An example of this is shown in case No. 19, where a single myeloma was seen in the upper third of the femur with no other evidence of tumour, but yet on sternal puncture almost 100% myeloma cells were found due to the needle striking a nodule, which was not found by the X-ray. Several cases of solitary myelomata are recorded, it is true, but only a very few can be considered authentic for the reason that tumours may be so small as not to be recognised by the ordinary methods of clinical investigation. At autopsy the solitary myeloma is thus naturally an even rarer event and even then I doubt its true existence, with the possible exception of the individual having died as the result of some accident and the myeloma being found by chance, the disease being yet in its early stages.

In/

In a very high percentage of all cases (90% according to Geschickter and Copeland) there is multiple involvement of the ribs, sternum, clavicles or spine, or any possible arrangement whereby these bones, individually or together, may be afflicted. Added to these may be tumour formation in the skull and/or the pelvis. These parts of the skeleton are involved in at least half the cases, and malignancy there is more common than previously supposed. In my series the skull was involved in just over 50% of cases and the pelvic bones in over 33% at least. The nodules may be very small and the real condition not at first realised. Finally the upper ends of humerus and femur may be affected. Other bones may exhibit tumour formation, but they are comparatively rare.

The site of tumour formation then is identical with the main distribution of red bone marrow. This in itself is surely<sup>a</sup> significant observation.

The size of growth will of course vary and no useful deduction may be made from its size alone nor from the number of myelomata found in any given case, though full recognition of the thorough autopsy should be allowed.

Other means of description are equally wide. Tumours are firm, or soft, sometimes painful, sometimes painless; they may be crepitant, pulsatile, or/



or may give a fluctuant sensation. Their appearance and dimensions may vary daily.

It is not difficult to understand this rather indefinite picture when we realise how vascular is the growth, how it erodes from within, gradually thinning out at the bone cortex, how it expands to surrounding tissues, and how it has a tendency to haemorrhage and necrosis.

In only one third of the cases in my series was tumour formation detected clinically.

#### Pulmonary Symptoms

There is no need to stress the pulmonary changes in myeloma. In individuals, mainly of middle age, a high proportion are already the victims of chronic bronchitis, whatever may be the disease which is instrumental in wearing them down. Myeloma, a wasting disease, encourages any chronic lung condition which may previously be present, and the myeloma patient's resistance being already poor, though previously having no chest complaint, is a likely subject for acute pleural or pulmonary inflammation. Particularly is this so terminally and the advent of inflammatory changes is of no more significance than in any other wasting disease or debility.

#### Nervous Changes

Nervous changes are most dramatically associated with the spinal cord and may be gradual or sudden/

sudden. When sudden the cause is collapse of the vertebrae and the distribution of damage will depend on the position of the vertebra telescoped, though extreme damage to the extent of paraplegia is not an inevitable result. If the collapse does nip the cord, all the miseries associated with cord trauma will follow - the flaccid paralysis, incontinence, formation of decubitus ulcers and so on (See Cases 6, 12 and 25).

Occasionally the onset may be very gradual due either to a slow collapse or perhaps, as in Case 8, to myeloma growth expanding into the theca. Such a growth in the covering membranes of the brain and spinal cord is perhaps rare, but it also occurs in Cases 22 and 25 in my series, and this site of tumour is very probably responsible for reports of thromboses in the intracranial sinuses, as made by Wallgren (1920) and Venturi (1901) for example.

If the cervical vertebrae are affected the scope of possibilities increases and paresis of the tongue, larynx and pharynx need no explanation.

Root pains, intercostal neuralgia and occasional herpes zoster, as mentioned by Wallgren and others, are all possibilities easily to be fitted into the general picture.

When the onset is slow and insidious due to gradual compression, the diagnosis may be very difficult, accounting for the mis-diagnosis of transverse myelitis which has been made on occasion, and the/

the clinical picture may be identical, at first some trivial bladder complaint, then weakness in the legs and dragging, loss of epicritic sensation and sexual appetite, followed by signs of an upper motor neurone lesion. Diplopia and failing vision, even actual blindness may be met, due to the tumour growth (Case 17).

In summary, no outstanding neurological symptom is typical and the patient, in his advance to death, may go through a whole gamut of sensations.

#### Gastro-Intestinal Symptoms

This is rather a vague heading, and to the reader may mean anything from wind to perforation of the bowel, and to any person confined to bed some kind of alimentary disturbance arouses no particular comment. In the section on amyloid further reference is made to gastro-intestinal disturbance as, in the opinion of a few, this peculiar form of degeneration may be more associated with diarrhoea for instance than hitherto held. It is difficult to criticise the suggestion as comparatively few tests for alimentary amyloidosis have been made in autopsy studies of myeloma. Further investigation is necessary and the idea should not be lost.

Terminal enterocolitis cannot be credited with any particular association with myeloma. It is known, however, that this condition is a little more common/



common in nephritis, and nephritis has its own peculiar association with myeloma.

Isolated cases of fatal haematemesis (Bertoye and Dechaume - 1904), melaena (Wallgren) and epistaxis (Geschickter and Copeland and others) are merely terminal and may be associated with the anaemia so frequently present. Also Geschickter and Copeland find an absence of free hydrochloric acid in most of their cases, but how often is this to be found in other conditions of terminal debility! As they point out, no correlation seems to exist between this clinical finding and the metastases of myeloma to stomach and duodenum so infrequently recorded.

The commonest alimentary complaints are nausea, vomiting and colicky pains, but Geschickter and Copeland together with Meyerding (1925), Wallgren and Jacobson notice that sometimes vomiting without nausea occurs. This is interesting, as the gastric disturbances have been associated with compression of the spinal cord and Martin suggests a gastric crisis analogous to that found in tabes dorsalis.

In my series no outstanding gastro-intestinal symptoms have been met.

### Fever

Fever is not uncommon in myeloma and at times there is no apparent reason for its presence. It has, however, been shown that mild inflammations characteristic/

characteristic of a debilitated state are frequent and this explains any transient rise in temperature, and it is usually due to bronchitis. There is no typical temperature curve like that seen in some cases of Hodgkin's disease.

## METASTASES

The question of myeloma metastases is a very debatable subject and the answer supplied varies directly with the conception of the disease. By metastases I understand the ability of a malignant tumour to invade the blood or lymph stream and thereby have carried to distant organs, as emboli of variable size, malignant cells capable of starting new growths similar to, or identical in structure to the parent growth though far removed from the latter. Thus, if on examining an organ not considered capable of producing primarily any given malignant growth, small emboli, or at any rate the presence of cells in the blood or lymph capillaries morphologically similar to those of the parent growth, were noted in that organ then it is justifiable to assume that the organ in question has been invaded by the method of metastases. In Cases 8 and 22 the presence of cells identical with the parent growth are found in such situations as liver, spleen, kidney, pancreas, lymph glands, dura mater and subcutaneous tissue. Surely this is metastasis.

There is, however, the conception that myeloma is of multicentric origin in the bone medulla, and Lubarsch had the idea that myelomata in such tissues as liver and spleen sprang from foci of myeloid cells already there, an individual growth.

It is conceivable that myelomata confined to the/



the skeleton may spring out from several isolated centres and a study of bones early involved in the disease shows the presence of nodules quite separate from each other but so may be the nodules of adenocarcinomatosis of bone. One point remains clear and that is that metastasis to organs outside the skeleton is comparatively rare even in the most advanced stages of the disease. Can it be that the metastases are inhibited in the other organs and the skeleton is more amenable to invasion? In all the cases of myeloma which I have seen there has always been one large growth, a parent growth, and the size of the lesions in the rest of the skeleton are much the same size or can be arranged in groups of size, and therefore the same age probably. This would indicate bone metastasis of a growth with an affinity for bone.

On the other hand, a malignancy like a reticulum cell sarcoma or Hodgkin's disease has no recognisable parent growth and in these diseases a multicentric origin is more easily understood. Hodgkin's disease is more selective and so may be reticulum cell sarcoma in the early stages, only to go completely wild later and invade any tissue.

Whatever may be the solution, it is legitimate to suppose that the growth starts at one place. This original node may then metastasise to receptive/

receptive tissues or the same stimulus may affect other parts of the same system and so a multitude of original growths may appear. The second argument does not satisfy me as a solution for the presence of myeloma in skin, kidney, liver and other organs. The odd invasion by myeloma of the pituitary in Case 7 is of course a direct invasion from a clinoid process and is easily explained. It would appear that both possibilities may well occur.

Thus Symmers (1901) thinks myelomata are neoplastic growths which spring from myeloblasts and that they are capable of originating growths in the extramedullary haemopoietic viscera by hyperplasia of pre-existing myeloblastic foci and in certain other tissues by metastasis and cell transplantation. This theory however is doubted by Pepper and Pearce (1917) who are especially concerned with metastases to liver and spleen. They summarise fifteen cases of myeloma with metastasis and consider that the theory of "homologous new formations" will not hold and that metastasis actually has taken place. Magnus Levy (1932) is also against the theory of multilocular system disease but supports the possibility of metastasing from bone to bone and giving the strongest proof for this, myelomata starting in the extremities.

In their review of the publications up to 1936/

1936 Geschickter and Copeland find 14 cases reported with metastasis to lymph glands, 10 to liver, 9 to spleen, 2 to tonsils and 1 each to thyroid, adrenals, lungs and ovaries. Duvoir, Pollet, Layani, Dechaume and Gaultier (1938) report a case with several subcutaneous nodules - metastatic tumours - and were only able to cite three other such in the literature.

It would appear then that the phenomena of metastasis in myeloma is not common except in the bone skeleton, when it is the rule.

In my series only Cases 8 and 22 show metastasis of plasmacytoma, but there is also persistent myeloid activity in the spleen and liver and the myeloma cells may have taken origin there. Case 22 is however strongly suggestive of metastasis, as myeloma cells are found in liver, spleen, kidney, pancreas, lymph glands and dura mater. There is metastasis in Case 25 but this was diagnosed as a myeloblastic myeloma.

In conclusion then, metastasis within the skeleton probably does exist, but outside the skeleton it is rare, but may be present.



### Summary

1. A general review of myeloma has been given.
2. The aetiology has been discussed.
3. The commonest signs and symptoms are pain, especially thoracic and lumbar pain, anaemia, loss of weight, bone deformity, fracture and clinical tumour.
4. Pulmonary, nervous and gastro-intestinal symptoms are secondary, but the nervous symptoms in particular may present.
5. Fever is terminal and not specific.
6. Metastasis throughout the skeleton is the rule, but to the other parts of the body is exceptional.

### SOLITARY PLASMACYTOMA OF BONE

This is a rare condition, but of recent years more and more papers are being published, mainly of single cases which in all amount to a very few in comparison to the reports of multiple myelomatosis. The age incidence is the same range as in the multiple form, but more rarely is Bence-Jones protein found. Chesterman (1936) found 13 cases of solitary bone plasmacytoma in the literature, including his own, which was the first recorded where the tibia was involved. There were eight cases where the femur was the tumour site, three for the humerus and one for the clavicle. The site of election was the shaft of the bone.

Pathological fracture is commonly the reason for seeking medical advice and this accident occurred in twelve out of the thirteen cases. Chesterman stresses the importance of the age. Bone sarcoma, Ewing's tumour, giant cell tumour and localised osteitis fibrosa cystica all occur at earlier age periods and are indeed more commonly diseases of youth, as opposed to middle age, though there is no hard and fast line.

Histologically the cell is the plasma cell type, the same as in the multiple form, and Chesterman was unable to find any other type of solitary myeloma of long bone in the literature.

The/

The treatment Chesterman recommended was curettage and bone graft.

Cutler, Buschke and Cantril (1936) report 18 and perhaps another 2 cases of solitary myeloma, including most of those reported by Chesterman, with short histories. In the series, however, are cases which sooner or later became multiple in type, which they classify as a separate group. It is doubtful if they were single at the time of investigation and in none was a sternal puncture done to find the marrow response. Case No. 19 in my series might have been classed in this group if a sternal puncture had not been done to prove generalisation of the disease before X-rays could detect it. Of the cases which show no signs of multiple foci there is nothing to indicate that they will remain so. They were discovered early mainly by the accident of a fracture. How many so-called solitary myelomata can exist without such an accident to precipitate a diagnosis? Small tumours or undetected tumours may last for months or years without detection but generally the diagnosis is only made at the multiple stage. There is no reason to suppose that the bone marrow is not showing signs of myeloma even at this "solitary" stage. Sternal puncture is required to help prove or disprove the validity of a solitary tumour, as even in the multiple stage frequently there is one outstanding large focus; and again, a negative result does/



does not verify the solitary feature of the tumour, as in the case of Rochet and Hutinel (1939).

Cutler thinks that in 3 of his cases the duration of 4, 9 and 10 years without signs of multiplicity is long enough to prove the solitary nature of the tumour. I disagree. Ten years is admittedly long, but even some carcinomata may linger a long time before metastasising. It is due to the individuality of that particular tumour. These cases are probably being observed and we shall learn in time if they keep their solitary nature. The group, if it exists, is a rare one. In only 2 of these solitary tumours was Bence-Jones protein found. The successful treatments were radium, X-ray, resection, amputation, and curettage, so that no definite therapy can be recommended. It is interesting to find that in one of the cases amyloid disease was observed at necropsy. Cutler is interested in the similarity of many of the solitary tumours to giant cell tumours in radiographic appearance.

Cutler does not mention the paper by Stewart and Taylor (1932), who also think that solitary plasmacytoma is a well defined clinical and pathological group, and quote Masson and Wolf's suggestion of subdividing plasmacytoma into simple plasmacytoma and malignant plasmacytoma. Stewart and/

and Taylor have one case in their series with 8 years good health after plasmacytoma of the maxilla. The treatment was operative but a nodule in the forehead, 3 months after treatment, disappeared with X-rays. This and the case recorded by Harding and Kimball (1932), in which a careful autopsy was done, would also substantiate the existence of the solitary type. Shaw's case (1932) was brought to light by the patient falling on the outstretched arm. The bone broke at the site of the tumour - middle third of humerus - and curettage and tibial graft was successful treatment up to that time of writing. Rogers (1929) found that X-rays were successful in his case, but they kept the reparative process in abeyance. In the multiple variety X-rays are of limited and at best transient value.

Peyton (1934) described two cases of solitary myeloma, but both became multiple prior to death, and there is no indication when the change took place. The grounds for considering the myeloma single were radiological. This is not enough, as I hope has been made clear in my section on radiology. It is interesting to find, however, that Peyton's first case was diagnosed as an angio-endothelioma, clinically and histologically. These tumours have been reported as involving the skeleton as a single or multiple lesion (Symmers and Vance - 1916).

Before leaving the subject, it should be observed that many of the tumours claimed to be solitary/

solitary are situated in the midshaft of long bones - a not so common site for large tumours of the multiple variety.

In summary, it is claimed by several authors that a solitary plasmacytoma of bone exists. The claim has not been definitely proved.

#### EXTRA-OSSEOUS PLASMACYTOMA

Extra-osseous or extra-medullary plasmacytoma is a division of plasma cell tumours to which little attention has been paid up till comparatively recent times and indeed few records of such cases are found in the literature. Ewing (1940), however, claims that such tumours occur fairly frequently and indeed we have now come to associate them with nasal and nasopharyngeal mucosal pathology, more from our reading in the greater works on neoplastic growth than from actual experience; that is to say, the actual diagnosis of plasma cell tumour of the upper respiratory passages is rarely made, though nodular infiltration by plasma cells - a manifestation of a chronic inflammatory response - is a commonplace.

One of the earlier discussions on these tumours was made by Claiborn and Ferris (1931). Up till that time the authors were able to cite 12 cases in the literature to which they added 2 of their own, making the total 14. The cases are fully described by them.

From/



From my reading of these cases and subsequent cases to be quoted later, the sites of these plasma cell tumours are variable and positions such as the following are mentioned.- Nose, nasopharynx, pharynx, uvula, tonsils, epiglottis, larynx, nasal fossa, turbinate bones, soft palate, eustachian tube, vocal cords, the air sinuses. Neighbouring lymph glands may also become involved. The symptoms are quite in keeping with the site of the tumour, i.e. difficulty in swallowing, nasal speech, hoarseness, epistaxis, tumour in the side of the neck, nasal obstruction with or without nasal discharge, frontal headaches, and so on.

These tumours are frequently multiple and may be sessile or pedunculated, and may involve a considerable part of the mucosa of the particular part involved.

Before granting these tumours a place in pathology and particularly a place among the myelomata, some obvious criticisms must be parried.

The skull and skull bones are notorious for the part they play in multiple myelomatosis, and it is not unusual to see little lumps protruding from the skull when the calvarium is involved.

Similarly, other bones of the skull may be affected and bony tumours may push their way to submucous positions, thus accounting for plasma cell tumours in/

in the upper respiratory passages, the disease showing no clinical manifestations elsewhere. It seems probable that this accounts for Rössle's case (1926) where the tumour had involved sternum, ribs and skull like the plasmacytoma of bone as well as making appearances through the clivus and in sphenoidal sinus and left antrum, soft palate and roof of the pharynx, involving the nose. Such a case cannot be classed in the extra-osseous group. Several such cases must have been seen by pathologists. It merely stresses the importance of autopsy or, if still alive, an X-ray of the skeleton, before such a claim can be made.

The next obvious suggestion is the confusion which may arise from plasma cell infiltrations forming tumour like masses, really part of an inflammatory process. I have seen several interesting biopsies, mainly sent from the Ear, Nose and Throat Departments, from the pharyngeal region where the tonsils and buccal mucosa are the seat of inflammation, long-standing, and where the tissue on section is extensively packed with typical plasma cells. There is nothing neoplastic about these. The plasma cell infiltration is truly remarkable, but the remains of the original tissue, modified certainly, can be recognised. Besides, bands of fibrous tissue are easily found, and the plasma cells are aggregated in massive colonies, not the homogeneous mass of plasma cells/

cells with little or no intercellular tissue so characteristic of the ordinary plasmacytoma.

The biopsy sent by the nose surgeon is generally very small indeed and frequently it is difficult to be sure whether the condition is neoplastic or inflammatory, and all pathologists are aware of the massive infiltrations of plasma cells which he may come across in his routine work.

Blacklock and MacCartney (1932) admit this difficulty, but in their case of a tumour occurring in the nasopharynx they favour neoplasm. The growths were multiple with relatively scanty mitotic figures and absence of amitosis... They classify their case as plasmacytoma. Tumours with similar characters were reported in the lacrymal glands by Hannes (1911). These may not be neoplastic, as Hückel (1927) cites Paschöff, Rados, Porkowsky, and Franke and Baurmann for suggesting that localised plasma cell tumours, which they have described as occurring in the conjunctiva, are of inflammatory origin. Again, a case of epulis described by Pirone (1909) and a tumour of the pleura by Klose (1911) were considered by their authors to be plasmacytoma.

In the literature opinions of the etiology of these tumours vary from inflammation in some form to true neoplasm, benign or malignant. Mattick and Thibaudeau/



Thibaudau (1935) claim that very few recurred after removal and very few looked truly malignant. The doubt as to whether it is really inflammation is continually in the minds of writers. This also concerns Campbell and Newton (1939) who, up to the time of writing, found 23 cases of this tumour recorded in the literature. This small figure is notable and contrasts rather with the statement made by Ewing that such tumours are fairly frequent. Intensive plasma cell infiltrations, I agree, and I repeat, are common, but the neoplasm, the plasmacytoma is decidedly not common.

However, it does, I am sure, occur and I claim Case No. 21 in my series to belong to this group. The tumour was localised to the tonsillar region and on section its appearance is definitely neoplastic, and the cellular picture is quite typical of plasmacytomata as described elsewhere.

Jackson, Parker and Bethea (1931) in their series record an interesting case of primary plasmacytoma of the tonsil removed 8 years before generalised bone involvement was detected. Biopsies from bone and tonsil were identical. An autopsy was done. They conclude that plasmacytomata may arise in lymphoid structures and subsequently involve bones; they may arise in bones and extend to lymph nodes; they may arise and remain in lymph nodes without further extension/

extension and may arise in bone without further spread. They would class plasmacytoma among the malignant lymphomata.

It seems probable though that several of the few claims for plasmacytomata in the nasopharynx are of inflammatory origin, sometimes due to syphilis, as in the case of Borri (1928). The tumour disappeared with syphilitic treatment. A similar case was described by di Vestea (1928).

Of the two cases that Claiborn and Ferris add to the literature in their review, I have little doubt that the first is a manifestation of inflammation. I have frequently seen in biopsies pictures similar to the one they display, and though it is not just to criticise a diagnosis on a photograph without seeing the original material, I would be inclined to consider their second case as inflammatory also. Case 21 in my series is much more typically neoplastic. Claiborn and Ferris themselves think that their first case may be inflammatory.

In summary then, I would say that there is a rare type of plasmacytoma peculiarly associated with the nasopharyngeal region, which is more frequently benign than malignant. This tumour may precede a generalised myelomatosis of bone. To be differentiated from these true neoplasms are chronic inflammatory states specific or non-specific.

## THE PLASMA CELL

As the majority of authors consider that most of the myelomata are composed of plasma cells, or at all events cells histologically similar to plasma cells, it is worth while considering the morphology, origin and occurrence of these much disputed entities.

### The Description of the Plasma Cell

The first description was made by Ramon y Cajal in 1890, who recognised the cell in syphilitic condylomata and gave it the name of the cyanophil cell, though it is to Unna that we owe the present nomenclature of "plasma cell" for the same cell, this structure being seen by him in the skin of patients with lupus. Unna made this description in 1891, a year later than Cajal, whose priority he afterwards recognised. Michels (1931) gives an interesting account of the discussion that followed the discovery, of the size, shape, staining reactions, protoplasmic appearance and nuclear shape and position of the new cell, and it is interesting to note the difference of opinion and indeed the heated argument during the next few years in which some well known observers took part. The more important opinions will be cited.

Cajal (1890) described a spherical or ellipsoidal structure varying in diameter from 7 to



14 microns. There was a deep staining cytoplasm containing vacuoles; the nucleus was eccentric and spherical, the chromatin network distinct. He considered it a special embryonic cell, as he could not associate it with the leucocytes, though later in 1896 he considered this cell a normal connective tissue constituent originating from lymphocytes and occurring in tumours, epitheliomas and papillomas, capable of fibroblast transformation - a theory subsequently to be dropped.

Unna for twenty years after his first description insisted that the most important characteristic was the deep basophilia of the protoplasm rather than the specific structure of the nucleus. It was because of this that he used the name plasma cell which had previously been given by Waldeyer (1875) to a quite different deep-staining connective tissue cell. The descriptive term of plasma cells was given because of the abundance of cytoplasm.

By contrast, at the same time Marschalko (1891) gave prominence to the nuclear structure. Unna's cell was unusually large, oval or cubic in form, and its protoplasm was faintly granular as well as deeply basophilic. This appearance he called "granoplasma" and it was reckoned specific. The nucleus he described as oval usually, clear, and composed of coarse chromatin strands. Mitosis was rare and binucleated.

binucleated structures were caused by amitotic division. The cell was derived from connective tissue elements and only occurred in pathological conditions, especially the chronic variety. It would appear that it was from this time that the unshakeable belief that plasma cells are necessarily characteristic of chronic inflammation originated, whereas it is quite evident that these structures are also seen in acute conditions, for example acute pericarditis, where there is no definite evidence of a chronic state.

Jadassohn (1891 - 1893) showed that plasma cells existed in lymph follicles and glands in man and other animals and stressed the significance of the chromatin pattern and eccentric position of the nucleus. He recognised no specificity in granuloplasm. Marschalko (1895) did not even recognise the granuloplasm of Unna and considered the morphology of the nucleus specific in opposition to the basophilia of the protoplasm, and laid down definite criteria.- the small round or oval nucleus with 5 to 8 distinct angular blocks of chromatin regularly arranged on the inner aspect of the nuclear membrane - a picture subsequently compared to a cartwheel by Pappenheim (1901); the eccentric position of the nucleus (later admitted by Unna); a perinuclear lighter staining area, and finally a spherical, at times irregular, protoplasm with no specific/

specific granuloplasm. Marschalko also considered these cells normal constituents of connective tissue though they did not arise from it but were formed from lymphocytes emigrated from the blood stream because, he argued, in foci of infiltrations the number of plasma cells was so great and the appearance so sudden that the origin from tissue elements was not tenable. On the other hand he considered that plasma cells, although a specific type of cell, could become transformed into fibroblasts, especially in new formed tissue, but he denies the presence of transitional stages between fibroblasts and plasma cells. In leucocytosis, plasma cells and transitional stages, whatever that may mean, were plentiful in the blood vessels, but in aseptic reparative processes plasma cells were never seen.

Though the views of Marschalko and Unna were at the time considered opposite, we now realise that together the descriptions give us the picture of what we now recognise as the plasma cell of chronic inflammatory tissue.

Since these discussions started numerous observers joined in the fray in an effort to reconcile the views; Marchand (1913) quite decidedly disproved the granuloplastic element of protoplasm as specific for plasma cells showing that this phenomenon was due to a transient cytoplasmic/



cytoplasmic basophilia present in other tissue elements as well as plasma cells. De Asua (1922) put forward as a solution that plasma cells were secretory corpuscles, the cyclic changes of which were seen histologically in four types of cytoplasm.-

- (1) pulverized and uniformly basophil (a resting stage)
- (2) crumbled or mottled (accumulation of secretion in granular form)
- (3) filamentous (a forerunner of plasmorrhesis)
- (4) peripherally serrated (stage of secretion).

These observations and suggestions are interesting, especially as the cell in question can apparently take on so many guises. The idea of secretion being a function of the plasma cell, when its appearance is compared to that seen in secreting epithelial cells, is by no means absurd, though not necessarily accurate.

Many workers were soon able to uphold the opinion of Cajal and Marschalke that plasma cells were normal components of connective tissue, some finding them in normal ovary, others in the omentum and others in the intestinal mucosa, to be closely followed by yet another spate of proof that they were found in the interstitial tissue of various organs and glands such as mammary and submaxillary glands, tonsils, liver, kidneys, bone marrow and lymphoid tissue. The work of three outstanding men may be quoted/

quoted in this respect, that of Maximow (1902, 1927, 1928), Ferrata (1923) and Downey (1911, 1928).

Maximow also denied their presence in the embryo, among other observers.

There is no doubt that the clear area lying to the inner side of the nucleus is reckoned by many to be a characteristic feature of the plasma cell, indeed, as has already been stated, v. Marshalko considered it an essential criterion, but Unna interpreted the phenomenon as an indication of a state of incipient atrophy due to a loss of granuloplasm, a theory supported by several subsequent observers. Slight modifications continued to appear in the literature but it was Maximow who first brought out the idea that the clear area was an attraction sphere containing a group of centrioles and demonstrated<sup>it</sup>/by iron-haematoxylin staining. This point of view was subsequently approved by Weidenreich(1909) and others. That this zone was of importance to the life of the cell was indicated some years previously by Cajal who had shown a Golgi apparatus there. More and more theories appeared and the perinuclear area was credited with the production of various granules, and equally varying chemistry.

Cajal also described cytoplasmic vacuoles as part of the anatomy of the cell. They varied in size and position and it is not unexpected to find that later these/

these were regarded as degenerative by Unna, de Asua and others, and as secretion globules by Weidenreich and Downey. Dubreuil and Favre (1914) were foremost in establishing the non-artefact nature of the vacuoles by using supravital staining with neutral red and in them were shown rod shaped structures - mitochondria. It was by supravital staining that Bloom (1928) was able to oppose the view of Cunningham, Sabin and Doan (1925) that plasma cells were related to monocytes.

It would appear that there is much less disagreement on the mitotic division of the cell; that this is a rare occurrence is an almost unanimous observation with the disagreement only of Schridde (1921) who considered it frequent in perivascular infiltrations. In my own observations mitosis has not been seen, at least in the case of the tissue plasma cell. Indirect division or amitosis and binucleated and trinucleated structures may be seen quite readily, for instance in inflamed tonsils. Michels agrees with Maximow (1902) in regarding the process as peculiar to old, degenerating cells, but it must be remembered that they refer to a cell as seen in perivascular infiltrations, a condition recognised as indicative of long standing infection.

When what at first appears to be a simple structure crowds the pages of literature with bursts of/



of contention, finally is given a recognised form, it must then be modified. . This is characteristic of practically all histological observations and the plasma cell is no exception, and so we may now consider the atypical cells. Many haematologists describe such variants and Pappenheim (1901-1920) who claimed that all lymphoid cells, whether of lymphoblastic or myeloblastic in origin, could become transformed into plasma cells, gave names to the intermediaries, making the situation highly complicated, nor was he the only one. Weidenreich (1909) and Downey (1911) more or less stated that plasma cells, as we know them, may come from the lymphoid series; the former observer spoke of a plasma cell condition, i.e. a phase in the lymphoid series, perhaps irritative, and the latter maintained that "plasma cells are differentiated from all types of lymphoidal cells including wandering tissue cells, mononuclears and fibroblasts".

#### Origin of Plasma Cells.

Several authors supported Pappenheim's view, among them Naegeli (1919) and Piney (1928) who recognised the occurrence of typical lymphoblastic plasma cells as originally stated by Hoderer (1896); further modification was made by Türk (1904-1912) who included his irritation forms among the plasma cells, forms considered by Naegeli to be pathological myeloblasts/

myeloblasts. Gruner (1913) supported Türk in claiming that these cells were tissue plasma cells which had entered the blood stream. The Italians, in particular, have considered the adventitial tissue of the smaller blood vessels to be the site of formation, - Savagnone (1908), Veratti (1905), Amato (1908), and an endothelial origin was put forward at the same time by Whitfield (1904), Mayon (1905), Huie (1907).

A brief summary of the views of origin of the plasma cell is recorded by Michels with the names of the advocates of each theory appended. In short, we have numerous names applied to blood cells and tissue cells, many of them indicating the same cell, from which the plasma cell is supposed to be derived, such as connective tissue cells, tissue lymphocytes, fibroblasts, clasmatocytes, wandering cells, adventitial cells, haemocyto blasts, haematogenic origin from emigrated lymphocytes, mixed origin from emigrated lymphocytes or pre-existent tissue lymphocytes, an origin from immature blood cells - myeloblasts and erythroblasts. A list of sponsors serves no purpose. In tissue culture of lymphoid explants and local lymphocytes Maximow (1922) found that plasma cells developed in two days.

To sum up the position is an unsatisfactory task. The general opinion, at the moment, of the origin of plasma cells is that they are derived from lymphocytes. There the evidence must rest in the meantime.  
Degenerative/

### Degenerative Changes

There are also extensive writings about the degeneration of plasma cells. It is not difficult to realise that an old or dying cell may take on a multitude of different forms. It is necessary to recognise these forms but it will serve no purpose here to give accurate anatomical descriptions of them nor to dwell on the staining variations. The appearances may be very confusing - may embarrass the investigator in any given instance and so disagreement on some issues is inevitable. Some of the more common degenerative forms will have to be dealt with.

Great attention is paid to the appearance of Russell bodies and granules of different shapes and colours, and speculation varies with the imagination of the writer. It is, however, necessary to remember that Russell originally described these bodies as parasites of cancer. One of the more interesting ideas is that of Jordan and Spiedel (1929), towards which Dawson (1929) was also inclined, declaring a haemoglobiniferous degeneration in that aborted erythroblasts become plasma cells and so gather into globules (Russell bodies) the haemoglobin with which they originally started life. The theory is interesting here purely as a possible explanation of myeloma of supposed erythroblastic type/



type occurring in bone marrow. Kindred (1932) carried out a study of the tinctorial reactions of haemoglobiniferous cells, Russell body cells, (I quote), plasma cells and lymphocytes of the albino rat by selective staining and found that the peripheral layer of plasma cells, lymphocytes, erythroblasts and haemocyto blasts contained substances of similar chemical composition to haemoglobin. It is very doubtful if staining reactions could go any great length in establishing the chemical nature of haemoglobin, which itself is still very much of an uncertain chemical complex. He also stated that plasma cells did not have the same reactions as fibroblasts, but this is in contradiction to Kingsley (1924) who claimed that plasma cells came from the fibroblasts of connective tissue as well as from histogenous lymphocytes and that the Marshalko type of lymphocyte was only one of several forms. The varying picture of degeneration, however, must be given serious consideration as nearly all reports are based on histological appearance and comparisons are made to better known structures. Krompecher (1898) describes a pathological degeneration especially occurring during inflammatory processes which brought about nuclear changes. The nuclei were vesicular, uniform in colour and had a less distinct chromatin network/

network with one or two central blocks which of course is not in accordance with the standard plasma cell of Marshalko but suggests a degenerate type. Vacuolar degeneration is also quite commonly found and numerous descriptions are made of this process. It is also frequently seen in Türk cells, and not infrequently in polymorph neutrophils - the so-called toxic polymorph. The emphasis placed upon it in the Türk and plasma cells of the blood is because the vacuole is helpful in deciding on the nomenclature of a doubtful cell. Homogeneous degeneration is mentioned by Michels among others but it is probably no more than a dying cell which has lost the power of cytoplasmic staining and in no way specific. Hyaline degeneration is the name given to the presence of bodies in the cytoplasm which may vary greatly in size and in their staining reactions. They are probably what are now rather loosely called Russell bodies, a view upon which there is some considerable agreement. It is quite clear then that plasma cells will show a very changeable picture in degenerative appearance alone.

#### Progressive Changes

Progressive changes are also attributed to plasma cells and the first of these recorded by Michels is the plasma mast cell - a rather elusive cell in which he himself believes in company with Marshalko, Pappenheim, Downey, Krompecher, who first reported it, and others. The process occurred through/

through an endogenous differentiation of basophil, metachromatic granules in otherwise unaltered plasma cells. The elaboration of other granules has also been shown, but Schridde (1921) declared that cells with a cartwheel nucleus and basophil granules should not be classed as plasma mast cells but as ordinary mast cells whose nuclei have undergone hyperchromatic changes as seen in other blood cells. This of course is important and precipitates the question.- Cannot all these nuclear changes be due to nuclear karyorrhexis and to changes in cytoplasmic mitochondria - degenerative changes indeed which are common to all tissue cells whether ectodermic, mesodermic or entodermic? I have examined many tonsils which were bisected immediately after enucleation and from one half smears made stained by Leishman's stain, and the other half fixed in Zenker, sections cut and stained by eosin methylene blue. The plasma cells were then compared. In the smears the angular blocks were scarcely evident but very obvious in the paraffin section. Fixation then clearly plays its part. Finally, Marshalko was well supported in his supposition that plasma cells were transformed into connective tissue elements. In modern times tissue culture workers refer constantly to this possibility, but it is difficult to obtain from them a definition of what they mean by fibroblast. Their cultures of fibroblasts/



fibroblasts do not look like those with which the pathologist deals and they admit how difficult it is to distinguish macrophage from fibroblast in culture - Why not residual primitive mesenchyme?

#### Function of the Plasma Cell

Suggestions as to the function of plasma cells are as abundant as in the case of the anatomical variations and probably are all speculative. Some of the collected suggestions are.- Absorption of chromatic material; formation of new nuclei; carriers of nutritive material; hypertrophy of connective tissue cells; carriers of iron and so perhaps related to the formation of fibrous tissue secretion; secretory corpuscles; elaborators of antitoxin and related to the immunization process; functional state of lymphocytes; reaction phenomenon, produced by metabolic changes, and phagocytes.

#### Definition of the Plasma Cell

Now I must make it clear what I mean by a plasma cell. The plasma cell may be found in the healthy individual but comes into greater prominence in the more chronic forms of inflammation. It is found commonly in the omentum, in the interstitial tissue of various glands, in the lamina propria of the intestinal mucosa and in the lymphoid tissue. It also occurs in the bone marrow and in general everywhere in the various connective tissues (Maximow in Cowdry's Special Cytology, p. 638, Vol. 2, 1932).

Even/

Even with the ordinary staining of the pathologist - haematoxylin and eosin - they are characteristic; with this staining and in the tissues the cell is round when free and subject to alteration of shape according to the interstitial pressure.

The characteristic features of plasma cells are especially manifest after staining with basic aniline dyes such as polychrome methylene blue. Pappenheim's methyl-green-pyronin stain demonstrates nothing that the basic aniline dyes cannot do.

The size varies from that of a small lymphocyte to several times that size. Plasma cells are probably feebly mobile as may be deduced from its presence in and among the crypt epithelium of inflamed tonsils.

The nucleus is rather characteristically the cartwheel or radkern nucleus. This arrangement <sup>may</sup> be due to the emplacement of the chromatin in block or strand form on the periphery of the nuclear sphere. If the section does not pass through the meridian of the nuclear sphere a block will be visible in the centre of the nuclear circle and will represent a hub while other blocks which may be caught by the sectioning will be on the perimetre and thus a cartwheel arrangement is produced. On the whole it seems best to consider the chromatin as diced or blocked and arranged peripherally in a sphere. The appearance is striking and easily recognisable.

The/

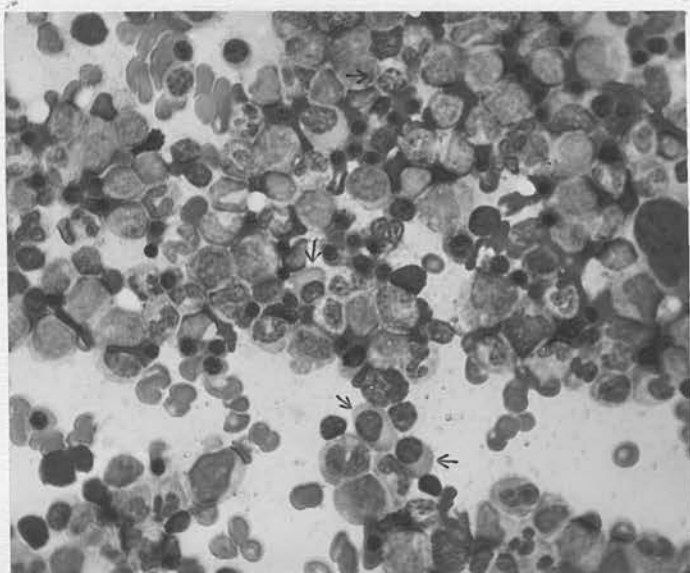
The cytoplasm of the fixed cell is abundant by comparison with nucleus. Its staining features are a help to identification. With haematoxylin and eosin the cytoplasm is not eosinophile nor yet is it basophile. It is amphophylic as if it had affinity for both the haematoxylin and the eosin with a resultant violet purple colour. This colour is not exactly homogeneous but is best described as finely granular or grained.

The nucleus almost invariably occupies an eccentric position in the cytoplasm. Still another character which is usually detectable in all or nearly all cells is an uncoloured or chromophobe area close up to the nucleus - a halo or "hof". If it continues right round the nucleus it is only as a thin rim on the outer aspect. On the inner aspect of the nucleus it is well developed and oval or circular in shape. This area is not vacuolar nor is it empty of structure, for it contains well known cell bodies, called centrioles. Mitotic figures are not found but binucleated or trinucleated varieties are not rare. It is not usual nor easy to see a nucleolus.

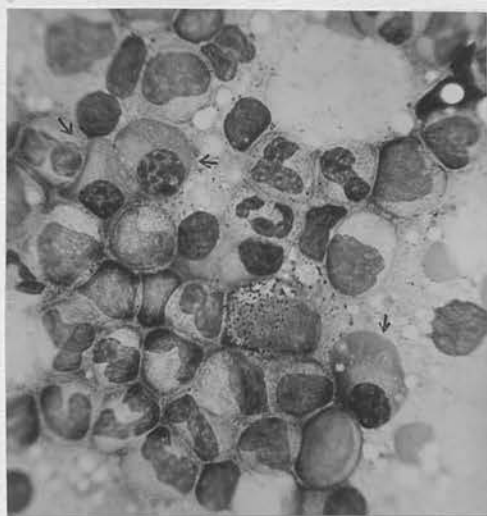
The question arises, what is the appearance of the plasma cell in the smear such as is made of blood or marrow? The smear cell is flattened out and takes on therefore a larger size than the cell which is/  
is/



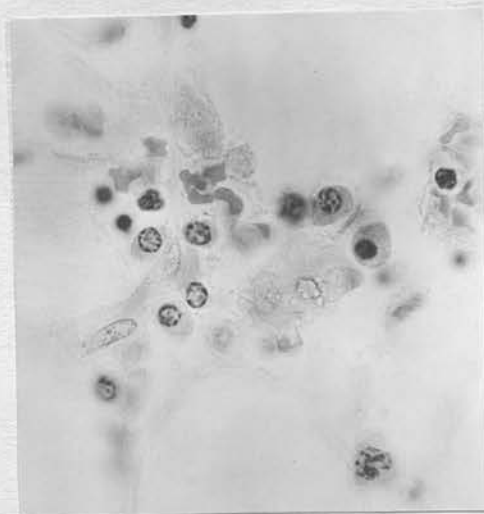
is found in tissues. For smears also the stains used are not haematoxylin and eosin. They are mostly stains of the polychrome series or those stains which furnish metachromatic colouration. With such cells and in smear the architecture of the cell remains nearly the same, the cytoplasm is clear or faintly granular and the nucleus often shows blocked chromatin, but just as often the chromatin appears as coarse bands tortuously traversing the nucleus. Vacuoles are not uncommon in these cells, especially the so-called blood plasma cells, but there is little evidence of phagocytic inclusions. Degenerative changes may occur in these cells with production of hyaline, rather eosinophile droplet formations.



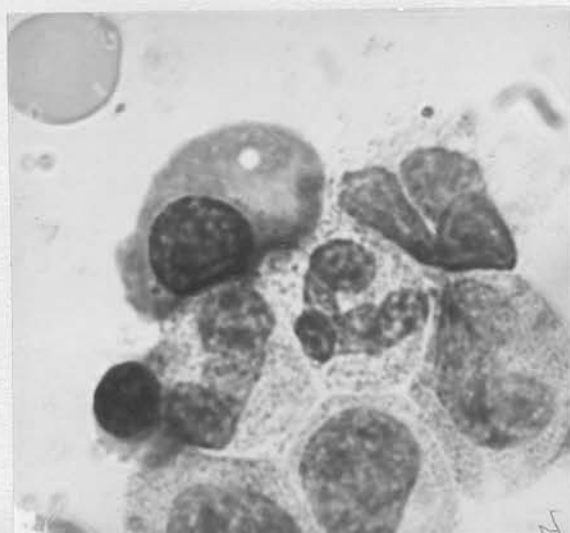
A. NORMAL BONE MARROW. x 400. Leishman.



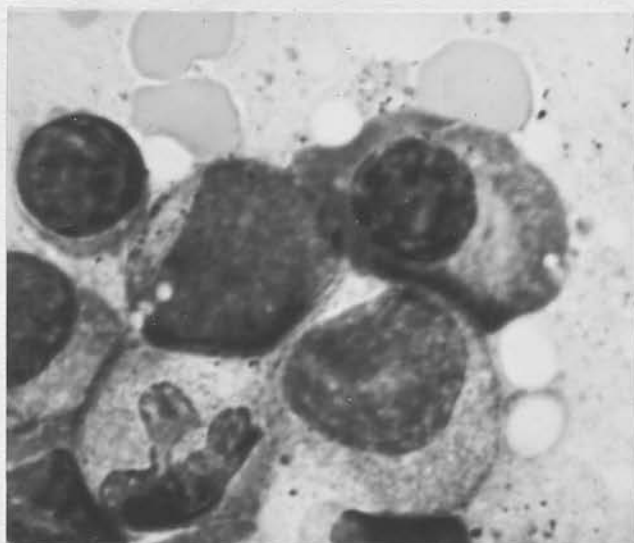
B. PARTIAL APLASTIC ANAEMIA SHOWING 3  
PLASMA CELLS. x 700. Leishman.



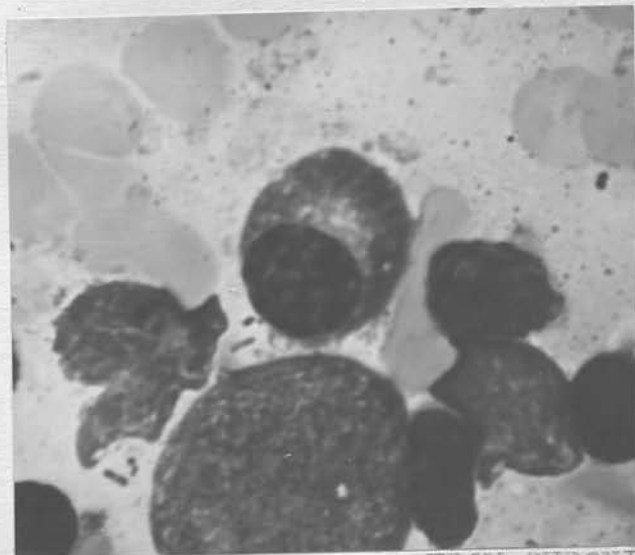
C. AGRANULOCYTOSIS. Paraffin Section. E.M.B.



D. PLASMA CELL IN SMEAR OF NORMAL BONE MARROW WITH LEUCOCYTES AND MYELOCYTES. Leishman.

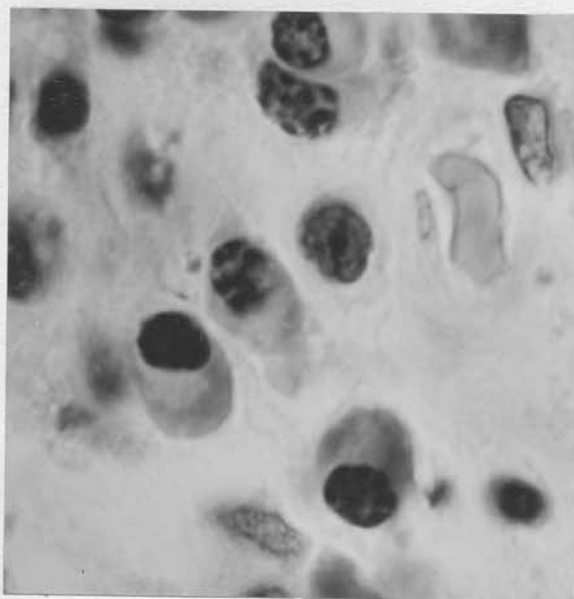


E. PLASMA CELL IN BONE MARROW OF PARTIAL APLASTIC ANAEMIA ADJACENT TO 2 PROMYELOCYTES. x 2000. Leishman.

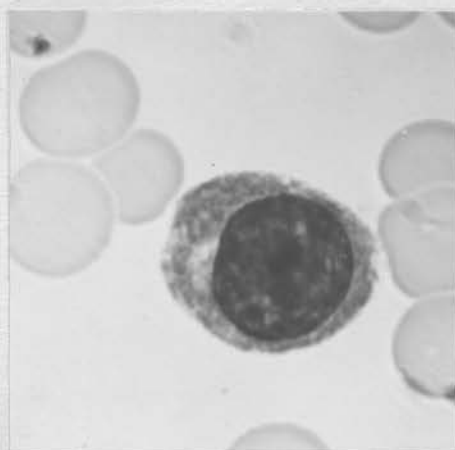


F. PLASMA CELL IN SMEAR FROM CHRONICALLY INFLAMED TONSIL. x 2000. Leishman.

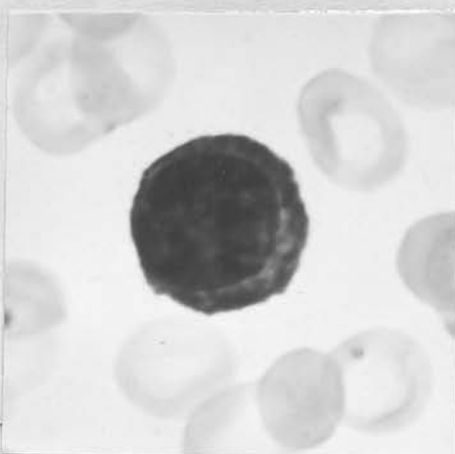




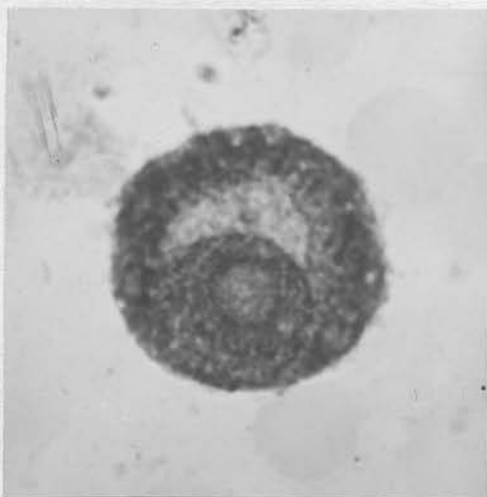
G. PLASMA CELLS IN CHRONIC INFLAMED  
TONSIL. Paraffin Section. x 2000.



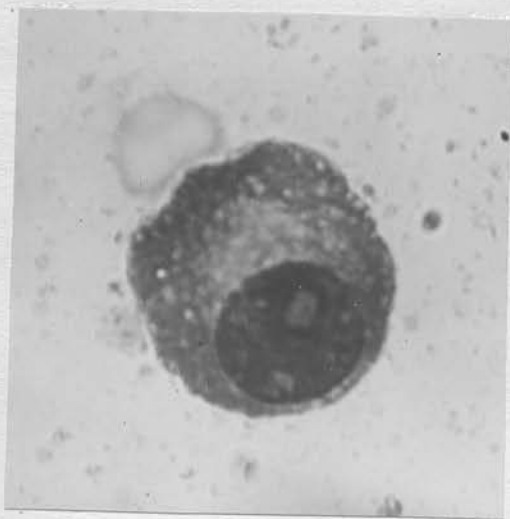
H. PLASMA CELL IN BLOOD IN CASE OF PLASMA  
CELL LEUKAEMIA. x 2000. E.M.B.



I. TÜRK CELL IN CASE OF MODIFIED ECK  
FISTULA. x 2000. Leishman.



J. PLASMA CELL OF PLASMACYTOMA (case 17).  
x 2000. Leishman.



K. PLASMA CELL OF PLASMACYTOMA (Case 19).  
x 2000. Leishman.

### The Plasma Cell in the Bone Marrow

The plasma cell has been discussed at some length but no special reference has been made to its relationship to the bone marrow and indeed its presence there is ignored by writers of first class papers on the bone marrow (Sabin 1928). However, Wright (1900), Hoffman (1904), Christian (1907) and Mallory (1914) write of the bone marrow plasma cell as a definite entity and normal figures are given by Segerdahl (1935) at 0.4% and more recently by Emile-Weil and Perlès (1938) at from 1 - 2%. With this latter figure I agree from my experience of several differential counts in normal bone marrow. It should be remembered that when the marrow is smeared and stained by Leishman's method the plasma cells is bound to be bigger than the one seen when a portion of the same marrow is fixed and embedded in paraffin and stained by eosin methylene blue. Otherwise there is no difference in the morphology between the cell in this situation and the plasma cell in lymphoid tissue and for this reason some photographs of plasma cells taken at high magnification and in different situations are shown in text figs. D, E, F, G and H.

I am interested in the sternal puncture picture as it is by this method that absolute diagnosis is claimed by Emile-Weil and Perlès (1938 & 1939) in myelomatosis/



myelomatosis.

As the study of these cells was made from smears they appear larger than those seen in sections and from the photographs it will be appreciated that they are generally oval but may be variable in size and shape; a spherical cell will be rendered ellipsoidal in the process of smearing in one direction; the nucleus is round and eccentric and the chromatin coarse but no angular blocks are seen. The cytoplasm is deep blue and almost always holds a paranuclear clear area. No granules are seen usually, but occasionally one or two eosinophil specks are just visible and vacuoles are not uncommon. When the cytoplasm is a very deep blue these cells are indistinguishable from Türk cells.

I consider the two cells to be the same, but in normal marrow the Türk form is seldom seen.

From my own observations of normal bone marrow smears and tonsil smears it is clear that the plasma cell is a normal entity of these tissues. No one can deny the possibility of the plasma cell's origin from almost any cell unit, but I think it much more probable that it is a direct descendant of some known cell unit of tissue and not a modification of several cells. Origin from the reticulo-endothelial cell has been postulated; I shall use this unsatisfactory term in the meantime. It is probably/

probably not a bastard form of other blood cells. In later pages there is more support for this proposition, particularly pathological support, and, as will be shown, it is possible that the reticulo-endothelial system produces the plasma proteins and we already know that plasmacytoma may be associated with a peculiar protein formation, Bence Jones protein. The tumour cell associated with this protein is very similar in appearance to a plasma cell when paraffin sections are examined and in other conditions in which the serum proteins are increased an increased production of plasma cells has been observed (Bing 1940). This in no way presupposes that tumour cell and plasma cell are identical. In his monograph on leukaemia Forkner (1938) diagrammatically indicates the possibility of the plasma cell being an immediate descendant of the "reticulo-endothelial cell", but this is hypothetical.

Text figure A shows the typical picture of a smear of normal bone marrow and in that field four plasma cells are marked by arrows. Figure B shows the marrow in a case of partial aplastic anaemia - the plasma cells are very clear, and figure C is a photograph of a paraffin section of the marrow in a case of agranulocytosis. The white and red series had practically disappeared but cells like plasma cells remained. That these cells are similar in appearance/

appearance is shown by the high magnifications, figures D and E, of plasma cells in normal marrow and partial aplasia. Figure F is of a plasma cell seen in a smear from an infected tonsil, and figure G the same tonsil after fixation and embedding in paraffin. The cells in the latter are smaller and the blobs of chromatin heavier. The difference in appearance is of course artefact.

Also taken at the same magnifications are figures H and I. Figure H is the plasma cell found in the peripheral blood of a case of plasma cell leucaemia to which reference is made elsewhere, and figure I a Türk cell in the peripheral blood of a young male adult who was suffering from toxæmia after a severe abdominal operation from which he subsequently died.

#### The Plasma Cell of Myelomatosis

From the numerous photographs of plasmacytomata included in this thesis as histological proof of the diagnosis, the malignant cell itself will be seen to be similar to those described as plasma cells when the tissues compared have both been embedded in paraffin; the clumping of the chromatin is particularly clearly demonstrated in the iron hæmatoxylin stained sections. The shape, the clear area, the eccentric nucleus are comparable and quite clear in the sections where the fixation has been careful/



careful, and the staining by haematoxylin and eosin good, or by eosin methylene blue, which, however, is not so permanent; but one outstanding difference stands clear, and that is the single eosinophilic nucleolus. This is not found in the ordinary plasma cells. The nucleolus belongs to a stem cell in haemopoietic tissue. The plasma cell originally defined was never regarded as anything but an end cell and it is doubtful whether it has a very obvious nucleolus. It is better to make a study of these myeloma cells from sternal puncture smears.

Figures J and K are typical of myeloma cells taken from the marrow by sternal puncture in different cases of plasmacytoma. There is no doubt some similarity between this type of cell and the bone marrow plasma cell referred to above. Reference to the Atlas of Osgood and Ashworth shows that these authors believe in a plasma cell series and their proplasmacyte is identical with the myeloma cell as seen in sternal smears, but this proplasmacyte is not far removed from a stem cell. The myeloma cell is bigger than the plasma cell (the magnification is the same as that for the plasma cell just described); it shows more marked cytoplasmic mottling, a finer chromatin mesh and a lighter blue cytoplasm. The paranuclear clear area may be a haze or a sharply defined crescent, or it may even be a circle. The nucleolus is outstanding and it is this cell which is characteristically/

characteristically found in and diagnostic of plasmacytoma in sternal punctures.

Other cells of the same type may be smaller or larger and monstrosities with 2, 3 or 4 nuclei are often seen, and mitotic figures are a regular feature, as the photographs of marrow in the plasmacytoma cases show (Figs. 69, 104, 105).

From these modifications in structure, the larger size, the presence of a nucleolus and mitotic figures and a fine chromatin mesh, there is a clear indication that the plasma cell of myeloma is a stem cell. This cell is quite typical and is unlike any other marrow cell and in contradistinction to the mature plasma cell, it is not seen in normal marrow. Apparently Osgood and Ashworth would call this cell a proplasmacyte - a normal precursor of the plasma cell. If that is so, it is very rare, and I have never seen it in normal marrow.

I would draw attention to the fact that the diagnosis of myeloma is only absolute when a nodule has been punctured; knowledge of the nodular distribution of myelomatosis will make this understandable. Between the nodules the marrow is quite normal or shows signs of secondary anaemia. However, on bordering the nodule the needle may manage to free a few myeloma cells which, on smearing the marrow, will give a low differential count of about 8%, for example as in Case 20, Fig. 108. The picture is not just/

just merely suggestive of plasmacytoma; it is diagnostic of it because, though plasma cells of the standard kind are seen in excess in marrows of aplastic anaemia, pernicious anaemia and agranulocytosis, this primitive cell is not found even in small numbers in any other condition than plasmacytoma. If, however, there is any ambiguity, another puncture should be done either above or below the first attempt in the hope of striking a nodule and so obtaining a characteristic picture, as was done in the case just quoted (Fig. 109).

#### The Value of Sternal Puncture

This method of diagnosis in myelomatosis is then of definite value, but due consideration must be given to the fact that the sternum is infiltrated probably only in 80% of cases; this figure is not so high as the one for ribs and lumbar vertebrae and it is based on autopsy findings. The figure may possibly be higher, because very small nodules could easily be overlooked, but it remains clear that an occasional negative result may be obtained from the puncture, and so more than one effort may be necessary and if still negative, the diagnosis is not finally ruled out.

It is interesting to note that Reich (1936) diagnosed a myeloma by sternal puncture when apparently performing the operation "just to see what the marrow looked like".

As/



As the sternum itself is not invariably involved it is quite clear that any claim to infallibility in sternal puncture diagnosis in myeloma is unjustified; but the probability is certainly high.

#### Sternal Puncture Technique

The technique I use is a very simple one. The skin over the sternum is prepared by cleaning with spirit. Cleanliness is essential and the hands are carefully washed before the procedure is carried out. A Sahli sternal puncture needle is used on which <sup>is</sup> a moveable flange which can be fixed at a given depth, depending on the estimated distance in the individual from the skin to the middle of the marrow. This prevents the needle suddenly plunging too deeply after it has passed through the outer table of bone. The experienced operator does not find this accessory necessary. The needle is kept in spirit until ready for use when all spirit is removed by washing it in normal saline. It is better to use saline as in the event of only a very little marrow being extracted - sometimes only as much as will be found in the barrel of the needle - it can more easily be extracted than if the needle were dry, and saline does not lyse the cells. The presence of any spirit is not only painful but spoils the marrow.

After/

After the skin has been cleaned  $\frac{1}{2}\%$  novacain is injected intradermally opposite the 3rd or 4th costal cartilage and just to one or other side of the mid line. The skin is injected and also the underlying muscle. The periosteum is then reached and is tender. This should be anaesthetised thoroughly and a short bevelled needle is preferable. The procedure takes five minutes.

The Sahli needle is then pushed through the skin until the periosteum is reached, and then by circular movements of the wrist the needle is slowly forced in. When the needle is piercing the outer table of the sternum a slight crunching feeling is recognised normally, but in cases of myeloma when the bone is diseased resistance may be only as firm as that of a piece of cheese. The needle then sticks firmly in the bone at an angle of  $70^{\circ}$  to the skin surface. The stillete is removed and a dry 20 cc. record syringe used and fixed to the Sahli needle. So far, if the anaesthetic has been properly done, there should be no, or very little, pain. If the patient is nervous the eyes should be covered, as he may be alarmed to see a needle protruding from his chest. When the record syringe is in position the plunger should be pulled out suddenly with as little movement to the needle as possible. A 20 cc. syringe gives good suction. This will give the/

the patient discomfort or actual pain lasting about a second. He feels a peculiar sinking feeling and gets rather a shock. It is better to warn him that he will probably feel this pain. After this the syringe is immediately removed, leaving the needle in position and the stillete is replaced. About 1 cc. of blood and marrow or even up to 5 cc. is usually extracted, though frequently only enough to fill the Sahli needle barrel, and the marrow is mixed with a very much larger quantity of blood.

The blood is not wanted. The best method is to empty the syringe contents into a watch glass and then pick out the little flecks of grey marrow, put them onto thoroughly cleaned dry slides and smear. The requisite number of smears are made and the remainder of the blood and marrow is put into Zenker's solution where after fixation paraffin sections of the marrow flecks are made in the usual way. The smearing and injection into Zenker's solution should be done as quickly as possible, as the blood is inclined to clot soon.

If enough marrow has been obtained the Sahli needle is removed and the puncture sealed by cotton wool and collodion. There are no pains and no after effects with this simple procedure, and the discomfort is only momentary.

Though the smears stained by such a stain as Leishman's/



Leishman's show up the marrow cells in a more pleasing way to the eye, the more reliable count is found in the paraffin sections, as in the sections the differential count is of greater value as we now have an appreciation of the interrelationship of the marrow cells. Both methods should be employed. The smear shows the intact cell, if a little flattened, and the section shows the relationship of the cells to each other.

From the myeloma aspect the only pertinent question is - are there any myeloma cells or not? If in any doubt try again at a different level, particularly if the X-ray picture is indicative of myelomatosis.

Should the sternum fail to reveal the diagnosis some other bone must be examined histologically and a biopsy specimen removed from a bone which the X-ray shows is diseased.

I have found that the X-ray photographs of the sternum may show that this bone radiologically is normal and yet a positive diagnosis is made by sternal puncture. The explanation is obvious; the nodules are too small to cause bony reaction or destruction but the needle hit one of them.

#### The Differential Count

I only wish to consider differential marrow counts in their relationship to myelomatosis, but Segerdahl's/

Segerdahl's conclusions from very extensive work on this subject are worth mentioning. She shows that the differential count is from 40 - 50% of the mean count, hence few counts will be significant, and unless the actually observed number of any cell series is greater than her mean plus 3 times the standard deviation or less than the mean minus 3 times the standard deviation, it cannot be significantly abnormal. With this view Kandel and Le Roy (1939) agree and they also stress the importance of the examination of clumps of marrow evenly and not too thickly spread. Normally there may be great variation in the counting and they, like others, are sceptical of recognising subtle diagnostic patterns in the differential count. With this opinion I agree, and a smear which merely shows fluid blood is useless. Flecks of marrow must be picked out and smeared and then many fields examined. In the case of myelomatosis it is usually definitely and undeniably positive or clearly negative, as frequently a nodule is hit and a "pure culture" of myeloma cells may be extracted (Fig.104). But the presence of very few myeloma cells recognised by a competent histologist are diagnostic without the unnecessary labour of a differential count.

The careful histologist may doubt the microscopic value of the solitary cell, but the myeloma cell of plasmacytoma/

plasmacytoma is unique in marrow smears.

Statistically the differential counts made are, when standard deviations are taken into account, not significant. With this view all such observations seem to point not to the abandonment of this method of counting - a purely defeatist attitude - but to the need for revision of definitions and characterisations of cells and possibly to the necessity of further embryological research in stem cells and their adult derivatives.



### Plasma Cell Leukaemia

I have given a fuller discussion of this debatable entity later on with references to the works of those who support it as a reality.

A glance at the photographs of case 24, one which is claimed to be plasma cell leukaemia, will show cells which are very similar to the myeloma cells just described. The leukaemia cells are slightly smaller and the nucleolus, though quite distinct, is less strongly marked. It appears reasonable to regard this as the same cell. Plasma cell leukaemia, if it exists (see page 164), is a very rare condition, but at the moment I wish to draw attention to the two types of malignant cell, that of myeloma on the one hand and that of this particular case of leukaemia on the other hand. The components of the two cells are the same.

Most pathologists think that leukaemias are tumours, widespread tumours with no particular limitation beyond their diffuse infiltration of the skeleton, such as has occurred in case 24. Myelomatosis on the other hand is peculiar in its nodularity and the association of leukaemia and myelomatosis is very exceptional - cases 22 and 23. In these two cases the nodular element is still present. There is no nodularity in case 24 and it has the anatomical appearance of a leukaemia. I therefore/

therefore consider that it is a separate entity and not a condition of leukaemic myelomatosis. A full discussion appears later.

### The Origin of the Myeloma Cell

It is time some effort were made to locate the origin of the myeloma cell of the plasmacytoma. The use of the words "plasma cell" has made unfortunate difficulties. There is the plasma cell so often found in inflammation which I do not consider is associated with myeloma. I have shown pictures of a plasma cell in the marrow, morphologically identical with the inflammatory plasma cell. It is a normal constituent of the marrow. Its relationship to the reticulo-endothelial system of cells is ambiguous.

There are different opinions in the origin of the blood cells, but I believe that all blood cells come from a common stem which has definitely adopted its haemopoietic "determination" from the primitive mesenchyme cell and which may conveniently be called a haemocytoblast.

The name of plasmablast has been given to a supposed precursor of that plasma cell seen in the normal bone marrow. It is extremely doubtful if the myeloma cell is a plasmablast. It is doubtful whether the similarity suggested by the term plasmacytoma should be postulated. The myeloma cell of plasmacytoma may be a modification of the reticulo-endothelial system of cells, an entity capable of so many guises that it comes to be very nearly primitive mesenchyme/



mesenchyme.

In this respect a paper by du Bois (1938) is interesting. Du Bois shows pictures of plasma cells of different stages seen in blood films and thinks them transition types of lymphoid cells and macrophages. Marrow films contained the same kind of cell. His was definitely a case of myeloma. Over the last three months of life the patient was receiving injections of carbon and at sternal puncture just before death no myeloma cells (with one exception) contained carbon. Reticulo-endothelial cells in spleen and liver had done so, it was discovered at autopsy. Macrophages did hold carbon.

Myeloma has been classified as one of the reticulo-endothelioses (R. Smith, 1938). However, there is no universal agreement to this. Emile Weil and Perlès agree with Naegeli that the myeloma cell of plasmacytoma is derived from the granular series and have no doubt of its myelogenous origin. Naegeli (1923) defines the plasma cell as a lymphocyte with abnormally strong basophilia of the cytoplasm. Piney (1924) considers the plasma cell to be lymphocytic and lymphoblastic in origin. Donati (1923) regards it as being derived from the haemocyto blast and therefore a potential blood cell. These references are of course concerned with the bone marrow plasma cell, which Wright (1900) thought was/

was the tumour cell in myeloma.

There is probably here a good deal of cross reasoning. One might argue that the myeloma cell is a stem cell with some plasmacytoid character but not to be identified with the plasma cell of the tissues. Whether the myeloma cell is myelogenous or lymphogenous is another question. Osgood makes the stem cell of these two series serve the same cell. Mallory (1914) proposes erythroblasts and megakaryocytes as a possible origin.

From the pure histological description it is very difficult, if not impossible, to localise the myeloma cell. It is also oxidase negative and so no help can be gained from this, contrary to the claim made by Forman and Warren (1917). In an histological comparison of six cases of multiple myeloma Christian thinks that the myeloma cell is like the bone marrow plasma cell (the pseudo-plasmacyte of Weil).

As in the opinions of the ordinary plasma cell, degeneration theories are numerous, but if a degenerative cell, then truly it has unusual life and determination in the propagation of its species.

#### Other Theories for the Origin of Myeloma.

Maresch (1909) suggested a granulomatous condition. This is unnecessary. Helly (1927), however, thought that the picture was one of anaplasia. He was the first to call attention to the /

the more or less normal haemopoiesis between the marrow tumour nodules and in some places between its cells. This certainly does occur and it may be interesting to refer to case 25 where the tumour is myeloblastic in type but the nearby marrow reaction is plasmacytic. Figures XXV 132 - 134 illustrate this and the question arises - can these plasmacytic looking cells be precancerous modifications of the myeloblast? By analogy I refer to a paper by Welsh (1930) who illustrates changes in epithelial cells before they become frankly malignant. If these "plasma cells" are precancerous then it may be possible that myeloma cells are modified myeloblasts. In the other autopsy material at my disposal I searched for other examples of this interesting finding, but without satisfactory result. I mention it without undue stress in view of the opinion just stated that the myeloma cell may be myeloblastic.

Morse (1920) was unable to accept myelomata as myeloblastic tumours because of the lack of association of myeloma with leukaemic states. This is no difficulty; we have aleukaemic leukaemias. Morse draws attention to the bone destroying power of the tumour and suggests that the plasma cells of the plasmacytoma may be heteroplastic osteoblasts.

The conception of myeloma could be simplified by adopting the view of a haemocytoblastoma with morphological/



morphological characters usually plasmacytoid but sometimes more myeloblastic or lymphoblastic.

Due to the ambiguity of the myeloma theories I would prefer to attack the subject of the plasma cell and its relationship to myeloma from a wide angle, and this requires a discussion.

### Conclusions

1. The plasma cell bears more than one connotation and these have been confused with one another.
2. The plasma cell of the inflamed tissue is an end cell and is the product of an unipotent, irreversible "determination" which links it with the lymphoid cell series proper, a series which includes that primordial residue which in recent times has received various names such as endothelial cell, reticulo-endothelial cell and polyblast, has certain end cell derivatives, one of which is a true plasma cell and the other a macrophage. The bone marrow plasma cell belongs to the same series.
3. The plasma cell of the myeloma is a bone marrow, a myeloid cell, not an end cell but a stem cell, capable of undergoing mitotic division, possessed of the other characters of a stem cell such as size, fine chromatin mesh nucleus and a nucleolus, and possibly possessed of some degree of pluripotentiality.
4. The myeloma cell should be dissociated from the inflamed tissue cell which has the priority right of being called a true plasma cell. The myeloma might be called a haemocytoblastoma but should not be called plasmacytoma.

### General Discussion on the Origin of Myeloma

The tumour known as myeloma and sometimes multiple myeloma because of its tendency to make widespread appearance in many bones, is usually so characteristic in appearance that it can be named at sight. This highly cellular tumour with its minimum of supporting fibrils and its close juxtaposition of cells is frequently called plasmacytoma because of supposed identity of appearance between its component cells and the "plasma cell" which is so familiar an object to general pathologists reporting on chronic inflammatory processes in almost any part of the body. I deliberately use the term "supposed" identity because my object in this investigation is to seek the grounds upon which the identity has been established and endeavour to maintain the negative opinion.

No one would deny that there are many points of similarity between the myeloma cell and what may, for purposes of this argument, be called the true plasma cell. It may be a platitude to say that similarity and identity are two very different things. In this investigation it is obvious that on the morphological side alone all possible morphological controls must be used and some attempt at production of the "negative instance" must be advanced, if only as guarantee of the bona fides of the/



the argument. Any collateral evidence which is not morphological will be utilised, but for the most part the argument will depend on the direct morphological answer to the question.- Is the myeloma cell a true plasma cell, and if not, what is it? The answer will depend to some extent on the comparison of the two cell types under the same strict conditions - section with section, smear with smear, and the same staining methods.

From the number of opinions stated on the plasma cell alone and also in conjunction with the morphology of the myeloma cell, it is very doubtful if it is possible to associate with accuracy the plasma cell and the myeloma cell, based entirely on microscopic observations, and all available evidence must be used if the identity is to be established. Much has been published and pictured to show the difference between the lymphoblast and the myeloblast for instance, to quote a chronic discussion in blood diagnosis. Here an opinion may be given with some confidence, if there is an accompaniment of differentiated cells to furnish the necessary support. That contention applied to our present problem suggests that a conjunction of myeloma cell and plasma cell would be sure ground for asserting that the cells were of the same lineage. Without such support it is doubtful if any pathologist would make his diagnosis on the/

the solitary cell.

Morphology, then, is deceptive in the hands of the inexperienced, and the confusion is all the more evident when some stages of the maturation of a cell may be similar to and even identical with stages of a totally different cellular unit more easily recognised as it grows older.

Most of the work on plasma cells which is entirely descriptive has been done on paraffin sections and the plasma cell in paraffin is somewhat altered from the plasma cell of the smear. This difficulty must be tackled straight away. By examining smears of chronic inflamed tonsils which, when put through paraffin, were found to contain large aggregations of plasma cells, the typical appearance of the ordinary standard plasma cell as seen in the smear was definitely established. Similar cells under identical laboratory conditions were found in the bone marrow smears, these cells also differing from the paraffin plasma cells of marrow as the smear and paraffin plasma cells differed in the same tonsil.

Now the plasmacytoma myeloma cell has been compared to a plasma cell, the comparison being made where the tissue described had been put through paraffin and without doubt these two cells are very similar. When, however, the myeloma cell and the plasma cell are compared in smeared tissue the difference/

difference is much more accentuated, though still similar, and it has been considered that the myeloma cell is a parent of the plasma cell - a proplasmacyte. This suggestion, however, is not in favour with many haematologists, and it is the haematologists who have added much confusion by the random application of the term plasma cell, and some of the blood cells are credited with entering a plasma cell phase. I see no need for this. Any experienced pathologist is aware of the pleomorphism of a cell type, even the normal epithelial cell of whatever function and in whatever tissue is capable of alteration of size and shape and cytoplasmic clarity, depending on physical as well as physiological reasons, and just because a type of blood cell may take on an appearance similar to a plasma cell it is no justification for calling it a plasma cell. Here I refer to the remarkable invariability of the true plasma cell stained haematoxylin and eosin found in the tissues which, even if it has undergone changes due to toxin decomposition or bad fixation, can be unerringly diagnosed by an experienced pathologist. I cannot then subscribe to the opinion that the plasma cell is merely an appearance common to the lymphoblast, myeloblast, lymphocyte and so on, merely because of microscopic appearance, nor am I impressed by the evidence put forward by the tissue culture experts, working/



working in an artificial medium, who after all depend on the microscopic appearance alone to put forward their argument. Many of them are not histologists. This absorption in a one-sided activity is apt to engender peculiar views and peculiar terminology. (The tissue culture expert has peculiar views on the fibroblast.)

The suggestion then that the myeloma cell is a proplasmacyte needs further investigation. The study of myeloma cells in smears shows some points very similar to the mature plasma cells under the same conditions. The chromatin network of the nucleus is similar in each cell and careful study reveals that it is fairly typical for the cell. The paranuclear clear area is also similar. Some sort of nuclear halo is characteristic also of the lymphocyte at times and the erythroblast, and it may even be seen in the lymphoblast and myeloblast, but in these cells it is never so much in evidence nor usually so typically crescentic as in the plasma cell and at times circular as in the myeloma cell. Vacuolisation is common to plasma and myeloma cell, but much less seldom seen in other blood cells and seldom looked for, e.g. in polymorphs. Morphologically all this tends to put true plasma cell and myeloma cell in a separate compartment.

What evidence is there to show that one is the parent/

parent of the other? Perhaps there is an answer in the case of plasma cell leukaemia included in my series. Studies of the sternal marrow smears of this case show many cells morphologically identical to the typical myeloma cell, but many of them may be slightly smaller. The parts, however, are to the eye the same. In profusion around these cells are standard plasma cells identical in appearance to the plasma cell of the normal bone marrow and the lymph node chronically inflamed as seen in a smear. The normal lymph node has no more plasma cells than the normal marrow, contrary to what would be expected if the plasma cell were just a modification of the lymphocyte, the lymph node being the factory for lymphocytes and presumably also for modified lymphocytes. But it has many more "miniature plasma cells" than the bone marrow because its chief cell, the small lymphocyte, can often be made out to be a replica on a small scale of the plasma cell of inflamed tissues. Does it appear then from the study of this plasma cell leukaemia case that the myeloma cell and the marrow plasma cell belonged to the same series?

Going on the principle that the more primitive cell has a nucleolus, the myeloma cell can be agreed to be a proplasmacyte or plasmablast, but the nucleolus, mitotic figures and size of the myeloma cell/

cell probably are more indicative of a different cell altogether. In the case of plasma cell leukaemia myeloma cells were not found in the blood as lymphoblasts are found in lymphatic leukaemia.

What then is the progenitor of the myeloma cell? I cannot see that mere morphology will be of any assistance in answering this question. Criticism may be made even for taking the argument so far on appearance alone, and, as I have already said, the adult cell is pleomorphic, how much more so may be the primitive cell? I doubt even if the careful studies of Osgood (1938) really can take us any further.

The discussion must then take a different form. So far I have indicated that the plasma cell is a real entity and not just a pictorial phase in the evolution of other blood cells, but no proof of this theory can be put forward on microscopic appearance alone.

The plasma proteins continue to be a mystery in formation and indeed to a great extent in their composition. Work will be quoted (p. 187) in support of the theory that they are produced by the reticulo-endothelial system, and I would restate here that there is no hard and fast delimitation between the different plasma proteins and possibly one may merge into another and vice versa. Can anything be obtained from an investigation into any condition/ or conditions where there is an hyperactivity of this function of the/



the reticulo-endothelial system, one of several credited to it?

9  
- For a long time Bence Jones protein has been associated with myelomatosis, though admittedly not by any means in every case and even in those cases which do show it, sometimes intermittently. However, the occurrence of this strange body occurs often enough, and by far the most commonly in myelomatosis, and one cannot but enquire if the cell type so characteristic of the disease is not connected with this protein's appearance, particularly in view of the opinions quoted that plasma proteins may be found by shedding from reticulo-endothelial and perhaps other cells. It would appear though that the reticulo-endothelial cell itself is not necessarily responsible for this physiological phenomenon, otherwise strange protein bodies would be associated with the other diseases grouped in the reticulo-endotheliosis. Reference to the section on Bence Jones protein will show that this argument need not be correct and there is ample biochemical evidence to show that probably many strange protein bodies are excreted albeit in small quantities, and for which but little search has been made. However, the reticulo-endothelial cell is another hypothetical cell created by definition and then established as an entity. This should continually be borne in mind, particularly/

particularly with reference to the following argument.

Bence Jones protein is probably a group not an entity, like the so-called albumen and globulin of the plasma themselves. Then if the reticulo-endothelial cell of the reticulo-endotheliosis does not produce a protein it is reasonable to suggest that a more specialised offspring has that faculty, and as it is an unusual cell or a cell vastly in excess of normality, it can be capable of producing a protein which is either unusual or vastly in excess of normal. There are many authors quoted who reckon Bence Jones protein to be a normal constituent of bone marrow. Microscopically whatever the myeloma cell may be, it is probably not the ordinary reticulo-endothelial cell itself and it may well be one of its many daughter cells. Indeed, the reticulo-endothelial cell has too many daughters to be anything but primitive mesenchyme or an "order of determination" very slightly removed from the embryonic pluripotential mesodermic cell unit. Bence Jones protein has been claimed to be isolated in other conditions quite different in pathogenesis to myeloma. These claims must be taken with reserve, and often there is no confirmation, but if the myeloma cell and its doubtful relative the plasma cell/

cell are merely abortive or modified myeloblasts and lymphoblasts surely we would expect to find the association of Bence Jones protein with the various leukaemias. We do, but very much more rarely, and there is no proper answer to the question - is it the same protein?

There is further evidence for the increase of protein production associated with the increase of plasma cells - the work of Bing, to which reference has elsewhere been made. In a series of widely different cases he found that where there was an increase in plasma globulin,<sup>and</sup> in general, an increase in the total plasma protein, the disease was accompanied by an increase in plasma cells, as for instance in different forms of inflammatory disease as well as myeloma. We know of the activity of the reticulo-endothelial system in inflammation - its antitoxin formation, phagocytosis, etc. There is an increase in the production of plasma proteins in the conditions of inflammation and other diseases cited in Bing's work and also in myeloma. Does this suggest a possibility of association between plasma cell and myeloma cell because of this common factor - increased globulin? The evidence is too slender.

In a modern conception of the evolution of the cells of the blood and also some of the tissue cells the so-called reticulo-endothelial cell is the patriarch. The myeloma cell has been described and we/



we find the nucleolus as an indication of its primitive state. Compare this to cousin cells in a similar state of development, for example myeloblasts, also containing nucleoli; they do not produce protein bodies or very rarely indeed in comparison to myeloma. This also helps to establish the myeloma cell as a real entity and not a modification.

Why does not Bence Jones protein occur usually in myeloblastic or myelogenous leukaemia? Perhaps the answer is found in the quantity of malignant tissue available for secreting in the respective cases. I doubt the satisfaction of this answer as no Bence Jones protein is found usually in advanced terminal myeloblastic leukaemia, where there must be a large amount of the bone marrow and medullary space infiltrated with neoplastic tissue, whereas Bence Jones protein may be present in the early stages of myeloma where the extent of the disease is reasonably localised in comparison to the myelogenous leukaemia parallel.

Apropos of the association of plasma cells with inflammation and with acknowledgment of the opinion that leukaemias may be caused by some infective agent, cannot myeloma with its primitive plasma cells be a response to an infective agent, for instance a virus, as the experimental work of Furth might indicate?

The/

The virus etiology stands or falls with the virus causation of tumours, but on morphological grounds alone the myeloma cells are not inflammatory cells.

### Conclusions

The myeloma cell is a primitive cell and it is associated with the production of Bence Jones protein. There are reasons, albeit slender, for supposing that the bone marrow plasma cell is related to the myeloma cell. The typical myeloma cell is not a normal constituent of the bone marrow. It has the morphological appearance of a stem cell and its behaviour is compatible with that of a malignant stem cell, perhaps a haemocytoblast. The bone marrow plasma cell may be one end result of the haemocytoblast.

### Plasma Cell Leukaemia

This extremely rare and debatable condition must be considered as it is entirely relevant, because, as I have shown, the same or similar cell holds the observers' attention as being responsible for the conditions of myelomatosis, myelomatosis with leukaemia and pure leukaemia each of the plasma cell type. This statement is based on histological comparison alone.

In my series case 24 is claimed to be one of pure plasma cell leukaemia, whereas cases 22 and 23 are considered to be of myeloma with plasma cell leukaemic manifestations, the autopsy reports in each bearing out the diagnosis though material in only one of the latter group is available. Similar to the cases of this group are those reported by Cappell (1929), and indeed case 8 may also be included, where there is marked myeloid metaplasia and leukaemic cells, apparently, seen in the liver and spleen sinuses (Figs. 22 and 24) as if present in the circulating blood. Cappell describes the presence of erythroblasts in the myeloid areas (compare case 8) and the primitive cells of the red and white series seem to transform to myeloma cells. This suggestion lends colour to the proposition of the myeloma cell being a stem cell, possibly a haemocytoblast, but in other places Cappell notices round/



round and oval cells pass by gradual transitions to elongated spindle cells which run in irregularly whorled strands with abundant intercellular stroma of fine reticulum and collagen fibrils, thus resembling sarcoma. This he admits is unusual.

There is no doubt that lymphocytes in lymphatic leukaemia may at times look very like plasma cells and case 24 may be considered a lymphatic leukaemia as the distribution of lymphocytes to the liver (Fig. 127), for example, is very similar to that seen in lymphatic leukaemia. A study of the malignant cell in sternal puncture smears (Fig. 125) and a comparison to the myeloma cell of plasmacytoma does not support this view in my opinion, and a comment has been added to the autopsy report.

In Forkner's monograph on leukaemia there are fifteen references quoted which are concerned with plasma cell leukaemia with or without plasmacytoma.

Aschoff (1906) was the first to find significant numbers of plasma cells in the blood of patients with multiple myeloma and in the same year Luchscher (1906) described a case of plasma cell leukaemia and Ghon and Roman (1913) had a case almost identical with case 24 in my series. Similar cases are published more recently by Piney (1924) and by Osgood and Hunter (1934).

Cases/

Cases of myeloma showing leukaemic manifestations though rare are not so excessively rare as the pure plasma cell leukaemias. Piney and Riach (1932) discuss myeloma and its aleukaemic and leukaemic forms and divide the pathological conditions concerned with the plasma cell primarily as.-

- (1) Multiple skeletal tumours - no striking blood changes.
- (2) Growths in bones and other tissues with a small number of plasma cells in the peripheral circulation.
- (3) Destruction of bone less striking but diffuse infiltration of marrow and other tissues, with a high plasma cell count in the blood.
- (4) High plasma cell count in the blood with generalised marrow infiltration like lymphatic leukaemia.

This is a good classification and suits the immediate purpose of the discussion, and straight away one cannot help drawing the comparison between myelogenous leukaemia and chloroma of the bone, and plasma cell leukaemia and myeloma of the bone, but myelogenous leukaemia and myeloma of the bone are much more common than chloroma of the bone and plasma/

plasma cell leukaemia. In this light then I am inclined to think that many of the myeloblastic and myelocytic myelomata reported in the literature, and two in my series, are really leukaemias (cases 27 and 28) showing an aleukaemic phase, though there is absolutely no reason to deny that each primitive blood cell may be capable of tumour formation. If that is so, why call them myeloma instead of chloroma, when the white cell series is involved? Tumour formation where the red cell series is concerned is exceedingly rare - reference to this is made elsewhere (Vance - 1916).

Now clearly the mere presence in the peripheral blood/ plasma cells or Türk cells, which I consider modified marrow plasma cells, does not constitute a state of leukaemia for it is well known that Türk cells appear in the blood for no recognisable reason, such as some toxic states, and most characteristic of all in German measles. To use Aschoff's word, the count must then be 'significant', and other evidence for a diagnosis of leukaemia should be present, such as is shown in stage 3 of Piney and Riach's classification, in which other tissues, e.g. lymph glands, are infiltrated.

The cases which I have show as significant a count as the cases recorded in the literature, claimed to be plasma cell leukaemia, all of which I have consulted/



consulted. The white count may be low or very high in any given individual and may be leukaemic or aleukaemic, varying from under 3,000 to over 60,000, and differential counts of plasma cells are so low as 5% (Hertz and Mamrot - 1913) or so high as 77% (Gluzinski and Reichenstein - 1906), and it is interesting to note that Bence Jones protein is not found in cases in which pure plasma leukaemia without tumour masses was met.

My experience of the plasma cell is that it is oxydase negative but Beck and McCleary (1919) record a case of myeloma with what are called plasma cells in the blood, having a possible oxydase reaction in percentage of 6.6. From this they infer that the plasma cell is myeloid in origin. I doubt if they were plasma cells - probably early myelocytes.

Mention is made elsewhere of extra-osseous myeloma originating from plasma cells which are so frequently found in lymphoid tissue and these cases may show leukaemic manifestations.

(1906)

These appearances then lead Lubarsch and Pappenheim (1907), Ghon and Roman, Jackson, Parker and Bethea (1931) and Patek and Castle (1936) to believe that there are comparable gradations in plasma cell tumours analagous to lymphomata. They may be single and benign or multiple and relatively malignant plasma cell tumours with or without changes in/

in the peripheral blood. Therefore the plasmacytoma is a pathological entity whose different forms are not distinct diseases but simple gradations in extent and activity of the same disease process. This supports the theory that plasmacytoma is a disease of the haemopoietic system (Miller and McNaughton - 1932).

### The Kidney Lesion

In the different reports on cases of myelomatosis it is common to find reference to kidney damage, and a good deal of research has centred on the ability of normal or abnormal kidneys to excrete Bence Jones protein. Opinions are various, each having a point of view worthy of comment. That it is of importance, however, may be judged from the fact that two of my cases were diagnosed as chronic nephritis to the complete exclusion of the myelomatosis, which was only brought to light by the pathologist.

The kidney lesion was first described by Mannhauser and Krauss (1920) who found a small white kidney with degeneration of the tubular epithelium - a condition which they called nephrosis, and, judging by their description, correctly. Authorities like Geschickter and Copeland also use this term with but little consideration for what that word really stands. It is not intended to criticise terminology, and, as the term nephrosis will be used frequently, more attention should be paid to the description than to the word.

In their series of 150 cases Geschickter and Copeland's figures at first sight are remarkable. Nephritis and Bence Jones protein were found in 61.4%; Bence Jones protein without nephritis 10.7%; nephritis/



nephritis alone 24.6%; and no Bence Jones protein nor nephritis 3.3%. From the point of view of pathology, however, this requires a different interpretation, and it may safely be concluded that nephritis means renal damage, of any sort probably. Indeed, these same authors state the age period of myelomatosis as being most commonly from 40 - 70, and from the experience of some hundreds of autopsies of bodies of that age group I might say that quite 61.4% show some renal damage, whatever the cause of death. Bearing these points in mind, some of the opinions on the kidney lesion in myelomatosis may be consulted.

#### The Excretion of Bence Jones Protein

By staining sections of kidneys with acid fuschin, orange G and Mallory, brilliant red, brilliant yellow and orange gold colours were obtained respectively, on what were considered to be Bence Jones protein globules and casts, by MacMahon and Magnus Levy (1936) after they had injected mice with that protein. The staining was not proved specific but was reckoned "a good indication". They found that Bence Jones protein may pass through a healthy kidney mainly through the glomerular tuft and sometimes by the tubular epithelium as well. When outside the cell it is harmless, but when taken up by the tubules it may cause necrosis, a reparable change/

change. This was the response to one injection. After two twice daily injections the entire tubular structure except the collecting tubules was severely degenerative. After two weeks of daily injections of a dilute solution of Bence Jones protein there was extensive focal contraction of the cortex with practically no damage to the glomeruli and vessels. There was also considerable regeneration and reconstruction of kidney tissue taking place simultaneously. The tissue changes were then somewhat similar to nephrosis and apparently Bence Jones protein could pass through a normal mouse kidney. A similar result was found by Krauss (1921) in rabbits. This was the conclusion reached by Hopkins and Savory with human tissue, by Miller and Beatjer (1918), Bell (1933), Taylor, Miller and Sweet, Walters, Hewitt (1929) and others, though Decastello and Kraus indicate that a nephritic kidney may be more permeable to Bence Jones protein than a normal one, a directly opposite view to that of Jacobson in a case he describes, but there is no satisfactory experimental evidence that the injured kidney is more permeable. Folin and Denis note frequent occurrence of hyaline and granular casts in myeloma cases with no clinical evidence of nephritis. It is possible that the casts were of Bence Jones protein.

The/

The actual nature of the Lesion

First of all there is plenty of support for the opinion of Thannhauser and Krauss that the condition is a tubular destruction or a nephrosis, though differing from idiopathic lipoid nephrosis as described by Müller (1905), Volhard (1918) and Epstein (1917). Bell is impressed with the presence of large casts, probably of Bence Jones protein, and thinks it likely that they are the chief cause of renal insufficiency in myelomatosis, as they cause atrophy. The usual evidence of renal damage is missing, such as albuminuria of the inflammatory type, haematuria, hypertension, etc., and structural changes may or may not be present. Miller and Beatjer's case is unusual in that it was of a chronic nephritis with oedema and high blood pressure with only Bence Jones protein in the urine - a most uncommon syndrome and the first reference in the literature.

Bannick and Greene (1929) attach importance to the examination of the urine for Bence Jones protein where there is marked albuminuria, secondary anaemia and no other evidence of renal insufficiency. The excessive albuminuria is also stressed by Walters. Bannick and Greene are, however, careful to note the fact that most of the patients are elderly and renal insufficiency is almost usual and probably due to chronic pyelonephritis or arteriosclerosis, but in the/



the latter two diseases marked proteinuria and marked anaemia are rare. The absence of hypertension, little or no oedema, nor retinitis, but some nitrogen retention builds up a syndrome for myelomatosis, together with the marked anaemia and proteinuria just mentioned. A similar clinical picture was drawn originally by Hammond (1924) as typifying the renal lesion in myelomatosis. Pyelonephritis is the only other kidney condition which can give a similar, though not identical, picture. Nephrosis and other forms of nephritis can generally be excluded by other means. Bell also indicated the frequency of arteriosclerosis and pyelonephritis due to cord compression, e.g. myeloma, and to prostate hypertrophy.

Perla and Hutner (1930) discuss the condition well and they quote Thannhauser and Krauss's case as the first case of "pure nephrosis" in myelomatosis recorded. Clinically the patient had the nephrotic syndrome. Casts were found in sections of the kidney; they were large and associated with an occasional giant cell. These authors label their cases as chronic nephrosis, as it were with apologies to Muller, Volhard and Epstein, and describe a syndrome similar to that compiled previously by Bannick and Greene. A very similar case was published by Rosenheim and Wright (1933) but they would/

would not agree with Bannick and Greene in calling the case one of nephrosis.

The presence of so-called giant cells and casts is interesting, as was seen in the cases of Thannhauser and Krauss, Lohnlein (1921), Kleine (1928), Mainzer, Bell and others. The last thinks they are formed by a fusion of macrophages entering the tubule from without. A very similar picture has been seen by me in some of my autopsy material and typical examples are shown in figures 16, 17 and 18. It will be noticed that in figure 16 the cells adjacent to the casts are identical with the ordinary tubular epithelium and it would seem that these cells have become unhinged and stuck to the casts. They do take on a flattened appearance, as is also shown, and can indeed look very like giant cells, but it is very much doubted if this can be considered a true bill (Fig. 17). It must be allowed, however, that these casts may act as a foreign body and are quite capable of stimulating foreign body giant cell formation. They are possibly made of Bence Jones protein, and when formed they must cause damage, as Bewley thinks, or perhaps increase the damage already caused by whatever the particular renal lesion might be. I am then in agreement with Forbes, Perlyweig, Parfentjer and Burwell (1935) who do not think that Bence Jones protein is toxic to the renal epithelium but that it causes disturbance of function by a destructive/

destructive process by means of the casts found. Long sustained excretion of Bence Jones protein in the urine may thus be expected to produce significant anatomical injury provided the quantity is large, but with a view to the age of the individual who is afflicted with myelomatosis the chances of having some kind of damaged kidney is very great and the Bence Jones protein casts embellish this previous damage. The glomeruli are slightly damaged sporadically in my cases and though the kidney appearances have a great deal in common with those described by the observers mentioned above, I am not prepared to call the condition one of nephrosis.

Amyloid disease in its association with myeloma may afflict the kidney and add to its excretory troubles.

Lastly calcification is sometimes found in the tubules in myeloma cases, as in my case 22. This has been found by Perla and Hutner and by Magnus Levy (1932) who considers that the deposition is due to the breakdown of bone. Bender (1902) noted calcification in the stomach mucosa and alveolar walls of the lung as well as the kidney in his case of myelomatosis, and Charlton (1927) writes of calcium metastasis to the kidney of his case.

In summary then it may be stated that there are possibly three main lesions in the kidney of myelomatosis/



myelomatosis. Firstly the so-called nephrosis associated with the excretion of Bence Jones protein and a low blood pressure with nitrogen retention; the name being chosen because of the tubular atrophy. It has no relation to lipoid nephrosis. Secondly, arteriolosclerosis, an independent kidney disease, and a scarred kidney due to chronic pyelonephritis, and thirdly, calcium deposits in the tubules due to destruction of bone and release of large quantities of calcium in the blood. It is felt that any claim to specificity is exaggerated.

#### Proteinaemia and Proteinuria

There are a number of pathological conditions in which changes in the serum proteins are to be found. Normally the range of total protein is from 6.5 - 8.0 grams %, with a relative albumen percentage of 60 - 70. The serum contains an albumen concentration of from 3.9 to 5.3% and a globulin concentration of from 1.9 to 3.4%. The fibrinogen concentration is about 0.25%.

These figures may be altered in various ways, but there are two main divisions; firstly, when there is an increase in the total serum protein and secondly, when there is a decrease - i.e. hyperproteinaemia and hypoproteinaemia. It is hyperproteinaemia which chiefly concerns us just now. A further subdivision may be made. Nearly all the cases/

cases of hyperproteinaemia are due to an increase in the globulin fraction, and particular attention will be paid to this.

Bing (1940) shows that there are many diseases known to be liable to association with hyperglobulinaemia, and some in which this condition has rarely or never been found before, and there are now several simple methods of demonstrating disturbance of the plasma proteins, all of which are expressions of the same basic principles. Amongst the better known of these is the estimation of the sedimentation rate of the red blood corpuscles. An increased blood sedimentation rate is considered an essential finding in myelomatosis. This is an exaggeration, but it is extremely common, and perhaps in myelomatosis is wrapped up a clue to the mystery of the origin of the plasma proteins and, as we are directly concerned with them, some time may be spent in tracing the previous history of hyperproteinaemia and its relationship to the blood sedimentation rate.

#### Early History

The earliest records of hyperproteinaemia go back to the Greek physicians, when great attention was paid to what English physicians centuries later recognised as "the size" or "buffy coat" of the blood. Its more classical name was the "Crusta Phlogistica", and this phenomenon was associated with several/

several diseases, particularly inflammatory ones. The size was due to a sedimentation or falling of the red cells, leaving a layer of serum on top. To-day we speak of an increased blood sedimentation rate and have reasonably accurate methods for its estimation. We know now that the blood sedimentation rate (B.S.R.) and hyperproteinaemia are closely related and some knowledge of the maintenance of the suspension stability of the blood is required.

#### The Blood Sedimentation Rate

In 1921 Gram discussed the variations in the sedimentation of the red blood corpuscles and the formation of the buffy coat on the blood. According to him the phenomenon depends on three main factors - the cell volume percentage, the percentage of fibrinogen in the plasma and the temperature under which the test is carried out. The fibrinogen percentage is lower in men than in women normally and in men there is a greater cell volume. The influence of plasma is great in producing any increase in rate and it has been shown that sedimentation is decreased with citrated serum instead of citrated plasma, but the lowering of the cell volume increases sedimentation both in plasma and serum. Again, the sedimentation rate is decreased when corpuscles suspended in plasma are deprived of fibrinogen, but when the cell volume is decreased the/



the sedimentation rate is increased.

Further experiment has shown that sedimentation is more rapid in citrated serum than in physiological saline but in both tests there is an increase in the rate when the cell volume is lowered. Pathological serum has a more rapid B.S.R., and parallel to this it has been shown that the addition of fibrinogen to a liquid causes a more rapid sedimentation of suspended bodies. From this it may be inferred that agglutination of corpuscles varies directly with the amount of fibrinogen present.

The fibrin content of blood is increased in nearly all infectious diseases, cancer, nephritis, pregnancy, polyarthrititis, and in other conditions possibly due to foreign proteids in the blood. Related to this suggestion is the fact that an increased B.S.R. is so frequently seen in myelomatosis with which we associate a foreign protein and anaemia to a greater or less extent.

The importance of fibrinogen in plasma protein pathology is indicated and must further be discussed, but now the work of Fåhreus (1921 and 1929) is particularly illuminating in leading us to understand the important part played by the other plasma proteins, physiological or pathological, in the estimation of the B.S.R.

This investigator found that if he suspended red/

red blood cells in fibrinogen, globulin and albumen, the sedimentation rate was much increased in the first, marked in the second, but only mildly increased in the third. To be noted also is the fact that fibrinogen is easiest precipitated by salts and forms a highly viscous solution, globulin less so and albumen least so. This may explain that the velocity is as a rule greatest when the viscosity of the plasma is high. This last conjecture may or may not be correct and from previous statements it is clear that an increase in plasma globulin can hasten the velocity, but a glance at Bing's figures will show that there is absolutely no relation whatever between the total amount of protein or the quantity of albumen and globulin and the B.S.R. Bing does not give a fibrinogen figure and it would appear that this protein may be of greater importance in the B.S.R. estimations than the ordinary clinical writings allow.

An occasional observation in making blood films in cases of myelomatosis is that of the presence of rouleaux of the red cells. It is of course found in other conditions such as pneumonia, and Fåhræus considers the lipoids of the plasma as well as the protein stroma of the red blood cells to be important, but of much less importance than the globulin increase. Besides, the blood gases, oxygen and carbon dioxide, play their part. Oxygen increases the sedimentation rate/

rate and carbon dioxide decreases it, facts which probably account for the low B.S.R. in cyanotic conditions - a modification which may occur, terminally in particular, in any condition.

### Physical Factors

It seems an obvious conjecture that surface tension and electrical charge influence rouleaux formation and experimentally it has been shown that the red blood cells are surrounded by an adsorbed water layer and this counteracts the electrical part, but Fahreus' experiments tend to show that globulins decrease the negative charge of the corpuscles - i.e. the self-repelling charge. In parenthesis, it may be recorded here that in a case of myelomatosis quoted by Reimann (1932) rouleaux formation was the first clue to the diagnosis. With agglutination or rouleaux, the axial stream of the blood has larger particles which flow faster and oust the white blood cells to the periphery, e.g. as in inflammation. Globulin increase not only augments an aggregation of red cells but of thrombocytes and thrombosis is related to an increased B.S.R. as in infections. This theory of aggregation is upheld by Cutler, Park and Herr (1938) who maintain that if no aggregation takes place the B.S.R. is slow no matter how marked the anaemia, the aggregation being a function of the plasma and is specific for that plasma. The specificity/



specificity is little influenced by the size, shape and number of cells in suspension, but the greater the aggregate mass the more rapid the settling and vice versa. These workers criticise the reading after one hour and recommend multiple readings throughout the hour to isolate the anaemia factor or "packing phase" from the blood sedimentation or "aggregation and sedimentation phases".

As it has been shown above, a diminution in cell volume or, expressing it another way, an anaemic condition due to a low red cell count, is capable of increasing the B.S.R. and it would seem advisable to make some correction for this, especially when considering myelomatosis which has long been recognised to have an increased percentage of the plasma proteins in the majority of cases. Such indeed might be the recommendation of Hynes and Whitty (1938) who have worked out charts for the correction of the B.S.R. in anaemia.

Anaemia is a common symptom in myelomatosis and a red cell count of 3 millions is not unusual, but in spite of this I have made no effort to correct for the anaemic state which must indeed be only a comparatively small factor in such large sedimentation rates as those recorded, though it must undoubtedly add to the rate, and so all figures recorded are those read after the citrated blood has been standing for/

for an hour in a Westergren tube.

It is fully realised that the different cases of myelomatosis show different states of anaemia but in view of the fact that the value of the correction for anaemia is contested, as well as being of doubtful aid, it has been decided to omit this purification (Cutler, Park and Herr).

There are other methods of quick estimation of hyperproteinaemia, such as the Formol-gel reaction and the Takata-Ara reaction, etc., but as Bing's paper so clearly demonstrates, there is no apparent association between the rate of sedimentation, the speed of the formol-gel reaction and the percentages of total plasma proteins or plasma globulin. A high B.S.R. may be associated with a small globulin increase or vice versa, and not even the different methods of estimation are related.

Thus the only true estimation of hyperglobulinaemia is biochemical, though undoubtedly an increased B.S.R. is a useful pointer towards a more detailed blood examination. Hyperglobulinaemia means more than 3.0 grams % globulin.

So much for the indications of increased plasma proteins, and at the moment some consideration must be given to the vexed problem of their origin as it is intimately related to the problem of myeloma.

#### Origin and Source of Plasma Proteins

In a review of the work done on this subject,  
Madden/

Madden and Whipple (1940) say that probably fibrinogen is wholly dependent on liver function and that albumen and much globulin is produced in the liver, and, contrary to numerous previous investigators, hold that the bone marrow is not an essential factor as a source of these proteins, putting forward as a proof of this observation that in aplastic anaemia, where marrow is in abeyance, plasma proteins are in the normal range. They agree though that globulin is usually responsible for the increase of proteins in hyperproteinaemia but declare that albumen may transform into globulin and vice versa; thus comes the suggestion that differences in the albumen-globulin ratio might be due to variations in production of normal globulins - the diet regulating production of globulin equally as well as albumen formation.

These workers do not regard the reticulo-endothelial system as a major factor in plasma protein formation.

I have attempted to show elsewhere that in a case of aplastic anaemia the bone marrow cells are indeed depleted to an extent even of being almost absent, but yet there remains behind a network of cells. It seems possible that what is left is the reticulo-endothelial network - a system of cells which is also found in the liver and other tissues. Thus, though the blood forming cells may be depleted and/



and the plasma proteins remain at a normal level, this is very far from proving that the bone marrow is not related to plasma protein formation as the reticulo-endothelial system is left nearly, if not entirely, intact. We are aware that in aplastic anaemia there is a relative increase in "plasma cells" in the bone marrow and there is an opinion that these "plasma cells" are directly descended from the reticulo-endothelial system which, as evidence below tends to prove, is probably the source of the plasma proteins and perhaps the "plasma cells", especially the more immature ones, may conceivably be capable of producing protein, particularly foreign protein such as Bence-Jones protein.

The liver also contains a large quantity of the reticulo-endothelial system and it is thus no small wonder that removal of it should seriously deplete the plasma proteins, but the experiment does not mean that the proteins are formed by the liver as an organ, but more by dint of its high content of reticulo-endothelial system.

In this vein Cutting and Cutler (1935) found that injection of Indian ink abolished the ability of the rat to replace acute loss of plasma protein - notice, "acute loss". Blockage of the reticulo-endothelial system does not kill the cells but it temporarily deranges them and this experiment is then very/

very suggestive of this system being the source of proteins.

It has been recognised for some time that antibodies<sup>are</sup> associated with the globulin fractions in the serum and also there is evidence that antibodies themselves are protein. That the reticulo-endothelial system is directly connected with the formation of antibodies is now almost an accepted fact (Zinsser, Enders and Fothergill - 1939). The link between reticulo-endothelial system and protein seems probable.

Sabin (1939) considers that the recent studies on the origin of the serum proteins point toward the reticulo-endothelial system and from her own work infers that the cells of this system normally produce globulin by means of a partial shedding of their surface films. A similar idea was held by Kleiger (1917) and others, who suggested that the blood proteins originated as a result of disintegration of leucocytes and that a foreign protein may be formed from the destruction of a certain type of abnormal cell turned out in excessive numbers. This is very apt when applied to myeloma. Bing (1937) could find no relation between the content of serum protein and the production of granulocytes of the bone marrow or the granulocyte content of the blood. In an array of different cases all associated with hyperglobulinaemia a feature was an augmentation of plasma cells and other/

other cells belonging to the reticulo-endothelial system within and outside the bone marrow; this Bing took to indicate that the globulin formation was connected with these cells.

The origin of the proteins has been considered mainly from the physiological point of view, but a great deal of work has been done by pathologists which may add further light on the subject, particularly in its relationship to myelomatosis and that peculiar protein body so often found in the urine, Bence Jones protein. Further opinions should then be consulted.

#### Pathological Proteins

Bence Jones (1848) is generally considered to be the first to describe the physical and chemical properties of a peculiar substance found in the urine and to which his name has been given. Ebstein (1915), however, claims that Heller described it before Bence Jones. Bence Jones reported on the urine of a case of mollities and fragilitas ossium, diagnosed by MacIntyre (1850), who wrote it up as such, but which was clearly one of myelomatosis, and from that time gradually more and more has been written about this substance with ever increasing modifications about its origin, secretion and significance. Bence Jones called it an hydrated deutoxide of albumen and found that as much of it was being passed in the urine as was present in ordinary blood.

Magnus/



Magnus Levy did more work on the subject than any other individual. He considered (1932) that its secretion depended upon nitrogen activity and was not exclusively endogenous as it could not be produced without protein intake, and indeed different kinds of food protein influenced Bence Jones protein (B.J.P.) production.

In the course of myelomatosis it was found that the excretion of B.J.P. increased, and remissions became rarer, until a cahectic state occurred and secretion decreased in accordance with the sinking of nitrogen metabolism; but complete disappearance of the protein had not been observed in true myeloma with a large excretion and in small degrees of proteinuria, only very rarely. Magnus Levy found

that ordinary urinary protein may be missing while B.J.P. is still present and that cessation of the B.J.P. or alternating with albumen only occasionally happens. A misdiagnosis in testing the urine may easily be made as a mixture of the two types of protein - albumen and B.J.P. - will give a different boiling point. True B.J.P. is precipitated at 50 - 57°C. redissolving at approximately 90°C., the figure varying with slight modifications in technique.

In spite of the loss of specific protein, probably there is no change in protein metabolism.

It is also recorded by Magnus Levy that in cases of high proteinuria with myeloma the amount of protein/

protein is one-fifth of that found in the tumour and in proteinuria without myeloma the bone marrow is generally anatomically diseased. This points to the suggestion that the bone marrow forms B.J.P. and of course other tumours in general do not show this protein, but still, proteinuria is absent in 20 - 25% of myelomata. Also in 1932 in collaboration with Freund, Magnus Levy found that the hyperproteinaemia in myelomatosis was due to fibrinogen and globulin increases, thus accounting for the increase in B.S.R., the rare quick blood coagulation and the sparse expression of serum from coagulated blood. With a moderate to high hyperproteinaemia B.J.P. secretion was not excessive, but if it did become excessive then the protein content of the plasma was low, so that it would appear that a marked hyperproteinaemia is incompatible with a marked excretion of B.J.P. In extra-medullary myelomata with B.J.P. fibrinogen in excess was found to be the cause of low temperature coagulation.

Magnus Levy (1931) also associates amyloid disease with B.J.P. and reckons that apart from tuberculosis and sepsis, amyloid disease is most frequently linked with multiple myeloma, an opinion not supported by several other observers. He goes on to say that amyloid may be present in large masses and then there is probably always B.J.P. in the/

the urine and this protein may also be in or near the bones and in the tumours. B.J.P. crystals were considered to be found in the amyloid tumours and it is suggested that hyaline substance, B.J.P. and amyloid degeneration are related. Though amyloid has been recognised for many years it is still not known what the exact composition is, but the accepted opinion is that it has a protein basis.

The analysis of B.J.P. has never been completed, though in sixteen different cases Magnus Levy (1936) found B.J.P. crystals, but he thinks that only part of the protein crystallises and that probably there is more than one substance comprising this body, but that it is the same part which crystallises. It should be noted that many other workers with equally diligent technique have failed to find crystals. In another publication also in 1936, the same author examined casts in cases of myeloma exhibiting renal insufficiency. They stained orange with Mallory's stain, as did isolated B.J.P. itself. Globules of globulin were found in the urine and a conjecture was made that this was the early stage of crystallisation of B.J.P., especially as many of these had changed into crystals after five years at  $2.4^{\circ}\text{C}$ ! Packalen (1939) had only to wait 4 - 5 months! The first record of crystallised protein in the urine was actually made in/



in Edinburgh by Noel-Paton (1892).

To estimate the presence of B.J.P. in the plasma is difficult, though it has been attempted, as will be recorded later. In view of this, it is interesting to read that Magnus Levy (1933) declares that hyperproteinaemia is exclusively due to englobulinaemia and thus may rise to 8%. Englobulin causes the majority of physical abnormalities in myeloma blood and B.J.P. has nothing to do with these abnormalities! Renal insufficiency is also reckoned not to be the cause of englobulinaemia.

Van Bonsdorff, Groth and Paekalen (1938) are not altogether in agreement with Magnus Levy's interpretations. They record the presence of a high molecular crystallisable protein in blood serum in a definite case of myeloma and they find several reactions which we have come to regard almost as inevitable in an absolutely typical case of myelomatosis, though admittedly some may disappoint. Pseudo-agglutination was particularly marked and was proved to be due to the patient's serum, the power of which was affected by lowering the temperature, and after clot retraction which itself was incomplete and slow. At refrigerator temperature two layers of serum formed, the upper normal, the lower, a pale yellow serum, and at the border of the serum levels there was spontaneous precipitation of protein crystals which were rather of/

of globulin nature but which in other ways were unlike albumen and globulin as normally found. Up till 1938 Mahle, Seed and Walker had cited fourteen cases of B.J.P. crystals in urine, always acid. Later Packalen's crystals occurred in alkaline urine.

It is unnecessary to enlarge on this very interesting if unusual case, but the conclusions are worthy of note. It is stated that the bone marrow plays an important part in plasma protein synthesis and therefore disturbance of plasma protein is an expression of bone marrow disfunction, but in spite of the increased plasma protein in the case recorded, no B.J.P. was found in the urine. The same authors give many references to support their thesis, but they are also careful to cite cases where normal or reduced values have been recorded.

Bannick and Greene (1929) are amongst several authors who record normal values and Chester (1933) published two cases of myelomatosis with decreased serum protein. He, however, observed a quick rise in the serum protein after a proper protein<sup>diet</sup> was given and assumed that the condition was due to a caenectic state. There was also a nephrotic atrophy of the kidney, a pathological condition which is discussed in its relationship to myelomatosis elsewhere. Hubbard and Case (1930) record that in their case of myelomatosis normal or low values for protein and globulin were found with B.J.P. in the urine, and/

and indicate that the opposite findings cannot be considered specific for, and diagnostic of this condition.

Hyperproteinaemia then cannot be said to occur in all cases of myeloma, though it is present frequently. Magnus Levy thinks that hyperproteinaemia only appears in severe and far advanced cases of myeloma. Von Bonsdorff disagreed with this proposition as in his case myelomatosis was little extended at the time proteinaemia was diagnosed. In all the cases which he quotes in which fractioning had been carried out, hyperglobulinaemia was present and in practically all the cases recorded albumen values were normal or reduced. This is in agreement with the figures of Bing (1940). Albumen values exceeding normal only are published by Magnus Levy - 5.7%, and by Veil - 6.2%. Fibrinogen estimation has seldom been determined and von Bonsdorff is one of few to give figures which show a remarkable increase.

In view of the presence of hyperproteinaemia so often associated with myelomatosis, coupled with the frequency of finding B.J.P. in the urine, numerous attempts have been made to find this proteose in the blood. The first attempt was made by Elhinger (1899) and he and Hopkins and Savory (1911) and Abderhalden (1919) demonstrated it by heat/



heat coagulation, but Macfarlane (1935), amongst others, was unable to obtain it. Numerous authors have observed that serum from myeloma patients have coagulated at 50-56°C., for instance in the process of inactivation while carrying out a Wasserman reaction. This was the unique method of diagnosis by Short and Crawford (1929), though B.J.P. was not found in the urine. A similar condition occurred in Case no. 14 of my series. Jacobson (1917) found in his case B.J.P. in the blood up to 7.8% before death, apparently due to renal damage. All authors who have had similar experiences do not hesitate in calling the protein precipitated at this low temperature B.J.P. This is an assumption, though it may be correct.

Perlzweig, Delrue and Geschickter (1928) and Magnus Levy found a protein in cases of myelomatosis with hyperproteinaemia, but did not think that it was B.J.P. The hyperproteinaemia was almost entirely due to euglobulin and fibrinogen, particularly the former, in Perlzweig's case, and the argument is put forward that as B.J.P. is chemically and immunologically quite distinct from serum and tissue proteins, it is possible to conceive it as a foreign protein in relation to the rest of the body. It is well known that in animals parenteral introduction of foreign protein produces alterations in the blood proteins/

proteins. These changes consist of an increase in the fibrinogen and globulin fractions, a decrease in the albumen and an increase in the total proteins.

By this we may reconcile the different opinions upon the origin of normal plasma proteins. It may be assumed that the B.J.P. is exclusively a bone marrow product acting as a foreign protein stimulating the liver to produce globulin and fibrinogen, but it is doubtful if the guess is justifiable.

Affection of the bone marrow of this kind may account for the hyperproteinaemia in some cases of carcinomatosis of the bones, a condition which has not infrequently accounted for the incorrect diagnosis of myelomatosis to be made.

Much has been written about crystallised protein and von Bonsdorff says that of the blood proteins albumen only is crystallisable, but B.J.P. crystals are known to have been found in the urine. In von Bonsdorff's case the serum separated into two layers and in Wintrobe and Buell's case the blood had a voluminous quantity of a substance which invariably precipitated on withdrawal of blood from the body. It was protein in nature and the patient had myelomatosis. The latter observers state that the temperatures of precipitation and solution of B.J.P. are not clear cut constants. Solution may be influenced by many factors, e.g. the concentration of protein/

protein itself, hydrogen ions, electrocytes and other compounds such as urea. In reheating the coagulum may be only partially soluble. They assume that B.J.P. is a class of substance and that it is impossible to establish the identity and exact quantity of foreign proteins such as B.J.P. in serum. In the case quoted B.J.P. must have been in a very unstable solution as there was mottling and blanching of the extremities and other signs of disturbed circulation - indeed a Raynaud's syndrome - yet there was no proteinuria. Where B.J.P. crystals have been found they have been hexagonal (Magnus Levy - 1936).

Wintrobe and Buell and von Bonsdorff and his co-workers obtained crystals in their cases and quote other similar observations; the latter workers also reckoned B.J.P. as one of several such foreign proteins. There was no proteinuria in their case perhaps due to molecular size. This increase in viscosity accounts for the incompleteness of clot retraction and expression of serum, not uncommon findings in cases of myelomatosis without proteinuria. This happened in case 17 of my series. Several similar observations are quoted by von Bonsdorff, among them those of Perlzweig, Delrue and Geschickter. It is interesting to find that in spite of the increased viscosity there was no increased blood pressure.

Other signs of peripheral vascular disturbance are/



are mentioned apart from Wintrobe and Buell's Raynaud's syndrome - thrombosis of the retinal veins for instance. Von Bonsdorff and his co-workers have reason to suppose that those disturbances in the peripheral circulation may contribute to the "rheumatic" pains frequently found in myeloma.

Animal experiments have been done to further the location of B.J.P. and Abderhalden and Rostoski (1909) have come to the conclusion that it is endogenous and a true protein, but may be a mixture, an opinion shared by Bayne-Jones and Wilson (1922) who also think that B.J.P. is immunologically different from proteins of normal human serum. This view was later reached by Bewley (1927).

Of the older workers, Ellinger (1899) was one of the first animal experimenters with B.J.P. and, by injecting it into a dog, found that it acted like a peptone, and both he and Askanazy (1904) demonstrated it in the blood, serous exudates and in the tumours themselves in cases of myelomatosis, as well as in the urine.

Fleischer (1880) was the first claimant to isolate B.J.P. from normal bone marrow but his success is doubtful. More recently, however, Meyler (1936) claimed definitely to have isolated it from normal bone marrow. He also found it in the marrow of cases of lymphatic and myeloid leukaemia, empyema/

empyema and in one case of severe fracture of the knee, i.e. in conditions in which there is a stimulus to white cell activity and increase of white cells. Meyler suggested that its rarity in leukaemia was purely a quantitative factor and concluded that the white cells played an important part in its production - myeloma producing such large quantities that it all could not be destroyed and was excreted by the kidneys and in all the larger quantities in renal insufficiency. This is quite reasonable as the myeloma age group corresponds with the renal insufficiency age group at their respective maxima. It does not explain how some cases with few myeloma nodules and apparently good functioning kidneys show B.J.P. in their urine, whereas older subjects with nearly every bone riddled with myelomatous tissue do not, or at the worst show just a trace, nor does it explain why it should occur, rarely admittedly, in cases of myxoedema. Experimentally Meyler produced it in rabbits' urine after intramuscular and intraperitoneal injections of emulsion of cow bone marrow. "Bence Jones-like" protein was found; criticism is obvious. All this wealth of evidence points to B.J.P. being a mixture of proteins.

The relationship between the bone marrow and B.J.P. is not at all clear and it is certainly not a monopoly of myelomatous bone marrow. Boggs and Guthrie/

Guthrie (1912) quote an instance where this protein was found in the urine of a case of metastatic carcinoma and one where it was not found in a case of diffuse myelomatosis. The same workers were the first to report its presence in the urine of a chronic myeloid leukaemic patient, this being the first account in the literature. It had previously been reported in cases of chronic lymphatic leukaemia. There is no report of its association with acute leukaemia.

Benzol was given to Boggs and Guthrie's cases and with the destruction of the bone marrow and its approach to a more normal condition B.J.P. greatly diminished and in one case entirely disappeared from the urine. From this they conclude that B.J.P. is not dependent on one disease but is a manifestation of disturbance in the bone marrow affecting endogenous metabolism. They have grounds for this conclusion but the rate and quantity of B.J.P. excretion may vary considerably without therapeutic modification.

Of the studies on the metabolism of B.J.P. the opinion of Hopkins and Savory (1911) is frequently quoted. Their experiments indicate that the protein is endogenous in origin and that it may pass through an histologically normal kidney. They were unable to find it in myelomatous tissue. Its peculiar place amongst proteins is due to its ability/



ability to redissolve at high temperatures because it enters into association with electrolytes - an explanation also put forward by Wintrobe and Buell the association compound only being stable at higher temperatures. Magnus Levy (1900) maintained that late in the disease B.J.P. behaved like an ordinary protein, the change being gradual. Though an anomaly, B.J.P. contained all the amino acids characteristic of a typical protein and its excretion was proportionate to the amount of metabolism more than to any other factor. It probably represented a stage, normal or abnormal, in bone synthesis. Hopkins and Savory, and Mainzer (1932) concluded, as did also Folin and Davis (1914), Walters (1921), Groat and Brewer (1929), that the diet did not influence it.

Jacobson quotes Simon's conjecture that B.J.P. is derived from the blood proteins through enzyme action of the abnormal plasma cells of the bone marrow. Bacterial action has been credited with a similar property in cases of B.J. proteinuria in miliary tuberculosis with no bone involvement (Austin). Miller and Baetjer (1918), however, say that it may occur in seemingly healthy young persons.

In their experiments on dogs Taylor, Miller and Sweet (1917) found that moderate amounts of B.J.P. could be catabolised but an excessive amount was excreted unchanged by the kidney. So previously had found/

found Allard and Weber (1906), but other investigators such as Decastello (1909) held that the kidney had to be damaged first, an exactly opposite opinion to that of Taylor, Miller and Sweet, who found that the appearance of B.J.P. in urine ceased when the kidney was injured with uranium nitrate and it was hydrolysed and eliminated as a proteose. Fatal results were obtained for which they blamed the proteose formed from the injected B.J.P.

### Summary

Enough has been quoted thoroughly to confuse him who would know the truth and it is evident that the variety of technique employed must lead to ambiguity, but all those experimenters who have found B.J.P. under conditions in which equally competent workers have failed, and vice versa, cannot all be in error, and so in summary one must infer that a motley of foreign proteins may be excreted in different diseases or that physical differences give an impression of chemical individuality. Doubtless they are all closely related to each other and may be excreted at different levels of formation, but their appearance would seem to be related to the formation and metabolism of endogenous protein, of the plasma proteins in the process of which some unknown factor or factors fail to play their parts, or play it to excess. How else could such a completely different series of disease such as myeloma, tuberculosis, hyperthyroidism/

hyperthyroidism and myxoedema, to quote a few, have this common failing in excreting such strange bodies in the urine? Can the bone marrow be blamed individually or in part? Yes, it would seem so, but probably only in part, and there may be a common denominator in myeloma and the leukaemias - the reticulo-endothelial system - in which diseases B.J.P. is found. There are conflicting views as to whether B.J.P. is normally found in the marrow or not; those who have crystallised B.J.P. are doubted by those who failed in their efforts to do so. However, some sort of crystals have been found, though admittedly very rarely, and it is not known accurately what should be the physical properties of the solution for such a phenomenon to occur. Were it known, probably more crystals would be found and more proteins might be isolated from the urine under different pathological conditions.

Whether this surmise is correct or not, the practical point remains that B.J.P. is not entirely characteristic of myeloma, though suggestive, and that its absence is equally of but little importance in the diagnosis. Its presence is very infrequently diligently investigated and we have little useful record of its appearance in the urine of cases quite unrelated to myelomatosis, for in the ordinary side-room tests, to look for such a body is not in the physician's mind, still less so in the mind of his clinical/



clinical clerk, and an early precipitation, perhaps very mild, could be easily missed in the heating test commonly employed. In the cases of myelomatosis which I have seen the urine has been tested for B.J.P. according to the methods indicated by Wells (1925), or rather sufficient of them to assure myself that the reactions I found were likely to coincide with those from which the diagnosis of B.J. proteinuria was made by others.

The main point I would stress is that myeloma and disorganisation of the proteins of the blood are related, and it is not unreasonable to suggest that the myeloma cell is responsible for the change and, as expressed elsewhere, there is the opinion that the myeloma cell and the reticulo-endothelial system are closely related, and there is strong evidence in favour of the reticulo-endothelial system being the source of production of the plasma proteins, both from physiological and particularly from the pathological point of view.

Lastly, only slight mention need be made here of the work of Macfarlane (1935), Kekwick (1940) and others, who study the behaviour of proteins, including those from serum and urine, in the ultra-centrifuge. It does not help us to decide whence come the proteins, but it does indicate the many kinds of protein which probably exist, a conclusion which has already been reached above.

### Amyloidosis

Already some reference to amyloid disease and its relationship to myeloma has been made. In 150 autopsies of cases of myeloma Magnus Levy (1933) records 37 with amyloid in the organs, and in 21 of these there was amyloid in the tumours themselves, and in 3 tumours of primary extra-osseous myeloma. The distribution was particularly in muscle, thus differentiating this from other forms of amyloid. Magnus Levy indeed recognised three distributions of protein metabolism - (1) Bence Jones protein, (2) Amyloid and (3) Englobulinaemia - and all these were considered to come from the bone marrow - blood cells and fluids - and the bone marrow was therefore the centre of protein formation, so playing a governing role.

In a review of the cases of myeloma up to the time of publication, Atkinson (1937) was able to find 40 out of 643, in which the presence of amyloid was found, i.e. 6.2%. Though I have found it in one out of ten autopsies, the figure is scarcely worth mentioning, but the interest aroused by the presence of amyloid, especially if related to Bence Jones protein, is sufficient to inquire a little further into the formation and distribution of this peculiar degenerative substance (Case 6, fig. 21).

Amyloid has long been known to be associated with/

with protein, as has, for instance, been shown by Jaffé (1925), who produced it experimentally after long continued injections of protein, deposits resulting from an acquired hypersensitiveness to the injected substance, or, comparatively, to foreign proteins, with the probable origin of the amyloid from collagenous tissue. In human pathology amyloid often shows affinity for areas of increased or abnormal cellular activity, for instance tumours or excessively active tissue. We are all aware of the usual distribution of amyloid substances in cases of chronic infection and how the liver, spleen, kidneys, adrenals, etc. may become involved. However, in myelomatosis both the usual picture and a somewhat different distribution is found. With regard to what has just been stated, it may be claimed that Bence Jones protein is a foreign protein, whatever its source may be.

Askanazy (1904) was the first to report the association of amyloid with multiple myeloma, an observation which has subsequently been affirmed. In a general survey of amyloidosis Rosenblatt (1934) mentions myelomatosis as one of the many diseases causing it.

The condition where amyloid deposits are found, but not in the usual organs, is styled systematised amyloidosis, and several articles are published on the appearance of this type in myelomatosis.

Michelson/



Michelson and Lynch (1934) found amyloid in the subepithelial tissues in their case of myeloma and quote Glaus (1917) for thinking that this type of amyloid was a true change due to myeloma, a suggestion which they consider reasonable as the leukaemias give generalised amyloidosis. The systematised form is also demonstrated by Weber, Cede, Stott and Pulvertaft (1937) and by Robertson and Brunsting (1936). Rosenblum and Kirshbaum (1936) found tumour-like amyloidosis in their case of myelomatosis. No tumour cells were seen in the amyloid masses, but it is by no means an unusual occurrence apparently to find atypical proteins in the urine in such cases, whether associated with myeloma or not. This may account for the many reports of Bence Jones proteinuria in different types of diseases which were really due to amyloid protein, but there are also reports of Bence Jones protein having the same staining reaction as amyloid and others where the amyloid had atypical staining, and thus it would appear that amyloid has as many phases as Bence Jones protein! Tarr and Ferris (1939) discuss typical and atypical amyloidosis with multiple myelomatosis and are particularly interested in deposits being found in the muscles and joints and in the associated presence of B.J.P. This makes them stress the presence of arthritis in myelomatosis and they suspect amyloidosis when a symptomatology not unlike rheumatoid/

rheumatoid arthritis is observed.

That the deposits may be large is borne out by Randall's case (1933) where intestinal obstruction was caused, due to amyloid infiltration of the small intestine, also in myelomatosis. Randall quotes Hueter (1910) and Glaus as having similar experiences. Paige (1931) found huge masses in the muscles round the shoulder joint and large masses are also reported by Stewart (1938). Even though such masses are exceptional, it is not rare to find amyloid in the intestine and Lubarsch and Borchardt (1929) believe that infiltration of the intestine causes paralysis of peristalsis. This may be relevant, as Geschickter and Copeland (1928) state that in myelomatosis alimentary symptoms are 20%, so that amyloidosis may be more common than supposed. Large deposits in the bone marrow, according to Magnus Levy, are rare but any tumour there would cause stasis and this he considers gives the tissues a chance to store amyloid. This probably does not account for all the physical factors, but in his classification of the forms of amyloid deposit in the marrow, Gerber (1934) puts myeloma as the commonest cause related to tumour, that is to say, apart from diffuse or generalised amyloidosis.

Amyloid is closely related to globulin and is supposed by Magnus Levy and others to take place in plasma/

plasma cells because it is so frequently found together with these. Other investigators indicate that the formation is in the reticulo-endothelial system, from experimental attempts to produce amyloidosis where the amyloid is frequently found mainly localised to cells belonging to this system. Smetana (1927) found that he could decrease the amyloid formation by blocking the reticulo-endothelial system.

There is then some evidence that plasma cells, reticulo-endothelial system, amyloid, plasma protein and the myeloma cells of plasmacytoma have some striking common factors, but it is difficult to claim that they belong to a pattern.



### Calcium and Phosphorus

Some alteration in the serum calcium figures from the average normal of 10 mgm.% to a reading above or below that mean is well known in disease of the bone, and very frequently there is an associated change in the serum phosphorus content. Indeed the estimation of the calcium and phosphorus in the blood is of very considerable aid to the diagnosis of some bone diseases most notably that associated with hyperparathyroidism where characteristically the calcium figure is raised and the phosphorus figure falls from its average normal of 3.5 - 4.5 mgm.%. This is admittedly helpful, but it is equally necessary to know the calcium and phosphorus balance, an estimation only too seldom carried out. I only wish to refer to these figures so far as they aid or hinder the diagnosis of myelomatosis. In the typical case of hyperparathyroidism the serum calcium is elevated and the phosphorus is lowered, but in focal osteitis fibrosa calcium and phosphorus figures are normal.

Osteoporosis is also found in hyperthyroidism and spontaneous fracture may follow. Probably the clinical features would point to the diagnosis but a similar osteoporosis may of course be found in leukaemia and, as my case no. 8 shows, in myelomatosis. In hyperthyroidism the calcium and phosphorus/

phosphorus figures are normal.

Osteitis deformans is seldom a difficulty in the differential diagnosis of myelomatosis and is mainly of interest at the moment because of the invariably increased phosphatase. Calcium and phosphorus readings are normal in the serum though the calcium excretion is nearly always greater than normal.

Carcinomatosis of bone for various reasons may be confusing in the differential diagnosis and here, whether osteoclastic or osteoplastic in type, the calcium and phosphorus figures are normal in the blood, though in the former the excretion of calcium is increased and decreased in the latter.

So far as calcium and phosphorus is concerned I do not think that other diseases of bone are likely to be confusing or, if they are, by chance, then the clinical or X-ray findings are such as to remove any confusion that might be felt merely by regarding the biochemistry alone and so no reference need be made to them.

Though I am unable to find the figures the biochemistry of cases of multiple sarcomata will probably be similar to one or other forms of carcinomatosis and there is nothing known about chloroma of any real value relevant to calcium and phosphorus. Similarly the xanthomatosis such as Hand-Schiller-Christian/

Hand-Schiller-Christian disease, occasionally a stumbling block to the radiologist, has normal calcium and phosphorus.

This leaves the field clear for a reckoning of the calcium and phosphorus figures of myelomatosis.

Metastatic calcification is not a new observation and was first observed in 1900 by Schur and Löwz in myelomatosis and Stewart (1938) cites Charlton (1927) as being the first to describe a case of myeloma with raised serum calcium; the figure recorded is 12.06 - 16.0 mgm.% and metastatic calcification was seen post mortem in the kidney tubules. McConnell's case (1923) is astonishing for the calcium found in the heart, alveoli of lungs, kidney, spleen and pancreas, and equally remarkable is that of Weisenbach and Lièvre (1938). In my series, case No. 22, there is calcification in some kidney tubules. It seems likely that mysterious cases of hypercalcaemia in which there was no autopsy nor biopsy performed and in which the X-ray picture was not typical were possibly myelomatosis. Such cases are quoted by Stewart, but still there is an impression that the calcium and phosphorus figures and ratio are normal in myelomatosis. Often this is not the case. Hunter (1935) finds that the serum calcium is sometimes markedly raised in which cases the calcium output is doubled. The serum phosphorus is usually normal and may even be normal when the calcium figure/



figure is raised, an important point in distinction between myelomatosis and osteitis fibrosa. There are cases, however, where the phosphorus is increased and unusually high figures are found where renal damage complicates the case. Of course there will be an increase in the phosphorus in osteitis fibrosa very terminally where renal failure is extreme and due consideration must be given to this. Stewart considers the calcium and phosphorus figures of value in diagnosis, especially in differentiation between myeloma and hyperparathyroidism, a misdiagnosis quite often being made between these two diseases (Gutman, Swanson and Parsons - 1934). The high calcium and normal phosphorus was helpful in the diagnosis of a case recorded by Caylor and Nickel (1933), very like one of hyperparathyroidism. A good example of this is in case 22 in my series. The serum calcium was so high as 15.9 mgm.% and there were calcium deposits in kidney and dura mater. Case no. 3 shows a reading of 16.2 mgm.% and in cases no. 18 and 20 the readings are on the high side of normal, or just above normal.

Phosphorus figures are not striking and all are high normals in my series where the estimation has been made with the exception of no. 15, where the reading is low. Case no. 5 is the only one in which the calcium and phosphorus balance was estimated with no abnormality found.

It/

It would appear then that only occasionally does the calcium figure rise and the estimation is of some small help in the differential diagnosis. The phosphorus estimation is generally normal or very slightly increased. This conclusion is in keeping with figures given by Ghormley and Pollock (1939).

#### Magnesium

There is very little mention of abnormality in magnesium in myeloma cases, but Weissenbach and Lièvre (1939), who give the normal figure as 1.8 - 2.2 mgm.%, find in their cases that the reading is much lower and varies from 0.8 - 1.5. In only three of the cases in my series has this estimation been made and no. 14 and 20 give low readings, whereas no. 19 has a normal figure. Three cases is too small a quantity on which to pass any opinion, but the observation is interesting and is worthy of further investigation. I am not able to suggest an explanation for the low reading, from what I can gather from the comparatively little work carried out on serum magnesium from the physiological point of view.

Phosphatase:

In all tumours of bone phosphatase estimation may be of significant value; it varies with the type of tumour and so the meaning of a high or low reading must be made clear. It is reckoned by Woodward, Twombly and Coley (1936) that the major portion of blood phosphatase is in the erythrocytes, though Roberts (1930) has found it in greater quantity in the plasma. Of the phosphatase in serum some comes from bone and some from liver, kidney and intestinal mucosa, as these tissues are rich in phosphatase. Serum phosphatase of non-osseous origin is raised by ingestion of carbohydrate, greatly raised by obstructive jaundice and lowered by starvation and ingestion of proteins. Of interest here is the phosphatase of bony origin and this is much increased in bone diseases associated with excess bone and osteoid formation. The rise of serum phosphatase in some types of bone tumour is apparently due to production of large quantities of the enzyme of the neoplastic tissue or adjacent periosteum and the removal of part of the enzyme of the blood stream. Increase of serum phosphatase may be of use in diagnosis of bone cancer, therefore, and also important in prognosis. It is consistently found that when the bone lesion is small, very slowly progressive, or chiefly osteolytic, serum phosphatase is low but widespread osteoplastic lesions, on the other hand, are/



are associated with high figures. The prognostic help of phosphatase estimation is indicated when a tumour such as an osteogenic sarcoma, which pours phosphatase into the blood, is removed; there should then be a fall in the figure, thus effectiveness of treatment and metastatic probabilities may be gauged (Franseen and co-workers). Myeloma is not a source of excess phosphatase and so removal does not affect it. Woodward, Twombly and Coley, however, do not think phosphatase figures of value in prognosis, nor do they agree that it is of value in pulmonary metastases. The readings are higher in a growing child, it should be remembered, because of the osteoid tissue and it is important to note that an increase may be found in callus formation, i.e. after a fracture, and this complication frequently accompanies myelomatosis. In a later paper Woodward and Higinbotham (1937) try to correlate serum phosphatase and roentgenographic type in bone diseases, several of which are mentioned. They declare that in myelomatosis phosphatase is normal and there is a slight elevation in phosphorus and calcium. In their opinion the phosphatase reading merely helps to confirm the X-ray diagnosis. It certainly must be of help in differential diagnosis and special reference should be made to hyperparathyroidism, because in a few of the cases of myeloma recorded here/

here, at one time during the clinical investigation the provisional diagnosis of parathyroid disease was made, occasionally at the instigation of the radiologist. Using the two sources of information together, it is logical to say that a normal phosphatase with an osteoplastic lesion must mean a slow growing and relatively benign lesion, though of course, as already stated, if osteoplastic and quickly growing, the phosphatase will be high. Again, if the phosphatase reading is high with an osteolytic lesion then there may be hyperparathyroidism (increase in blood calcium and phosphorus will also help) or possibly an osteoplastic disease elsewhere or an early highly malignant osteogenic sarcoma.

Hyperparathyroidism is the most likely mistake to be made where the lesions as seen on X-ray film have a cyst-like appearance like myelomata, particularly solitary myelomata, before fracture has occurred. When fracture complicates the scene then the phosphatase readings can scarcely be so reliable, as callus forms often quite well, especially with the assistance of deep X-ray therapy. Whatever may be the permutations and combinations, high phosphatase readings indicate bone disease. Simmons and Franseen (1935) also stress the value in diagnosis of phosphatase estimations and record that in eleven cases of plasma cell myeloma only one reading/

reading was above normal, whereas multiple metastasis in carcinoma and generalised fibrosa cystitica have readings well above normal.

Franseen and McLean (1935) estimated phosphatase in the plasma and the tumour tissue of six cases of myeloma and found it normal in each case. These authors maintain that the enzyme is synthetised by osteoblasts so it is not surprising to find it elevated in the osteoblastic type of osteogenic sarcoma, and they also favour the usefulness in phosphatase readings in prognosis - the figure for instance falls with the removal, or other successful treatment, of the tumour and rises with a recurrence. A temporary fall is found after X-rays whether the treatment will ultimately be successful or not. It would appear then that, apart from formation of osteoid tissue as in a growing child, rickets and jaundice, elevation of serum phosphatase mainly suggests osteitis deformans, generalised osteitis fibrosa cystica and extensive metastatic disease of bone and osteogenic sarcoma. This is a good example of cells which have become neoplastic continuing to produce their physiological secretion - evidence of synthesis of an enzyme by a neoplastic cell.

These facts have been verified by several other workers and Kay (1929) is of the opinion that lesions of bone involving a large portion of the skeleton are accompnied by a rise in the amount of phosphatase



phosphatase in the plasma. In osteitis deformans and osteitis fibrosa the increase may be four to twenty times normal, and Roe and Whitmore (1938) are aided in the differential diagnosis of a case of a lymphoid type of aleukaemic leukaemia with extensive involvement of bones, in which the phosphatase was normal, and one of hyperthyroidism.

Kay (1928) also found that there was a relationship between the kidney phosphatase and bone growth, and in a very comprehensive paper on the interpretation and significance of serum phosphatase in diseases of bone Bodansky and Jaffe (1934) show that renal dysfunction increases the value but that senility, malnutrition and anaemia lower the value, and that high leucocyte count may be associated with a slight increase. These authors presume that phosphatase is an expression of the specific activity of bone. The increase of phosphatase in renal dysfunction is perhaps worthy of more than a passing reference in view of some of the renal changes shown in the cases described in this thesis.

There are different methods of estimating phosphatase and so ranges of normal will vary; for instance Kay and Bodansky (1933) use different methods of estimation. The test used in my series is a modified form of the one employed by Kay, as used by Dr C.P. Stewart in the Royal Infirmary, Edinburgh, and the range of normal is from 28-40 units.

My/

My own experience of the phosphatase readings in the cases of myeloma which I have seen is that nearly all are raised, indeed it is the exception rather than the rule that they are not raised. This may be due to a variety of causes such as fractures or renal damage, but it does not seem to be related to the extent of the skeletal lesions. Thus in 10 cases of myeloma in which phosphatase was estimated 8 showed an increase and in cases No. 7, 14, and 19 the rise was very marked. In case 15, in which the phosphatase figure was normal, not only was the disease extensive but there were several fractures, as reference to the X-ray photographs will show. In my experience then the phosphatase estimation is ambiguous, but I am much more impressed with the elevation of the figure than with its normality.

Other Biochemical Findings.

As the table shows several other biochemical investigations were carried out, but nothing definite was found and in this line there is no alteration characteristic of myeloma. Ghormley and Pollock indicate that the blood uric acid may possibly be significantly raised. In the few instances in which this investigation was carried out in my series of cases no such claim can be made. Case 20 is the only one of 6 cases in which the uric acid was estimated that shows an increase - up to 5 mgm.%. Whether this occurred after X-ray therapy or not is difficult to say.

The blood urea is not considered significant, as any elevation in this figure can nearly always be accounted for by kidney disease, arteriosclerotic or parenchymal.

Other biochemical findings are given in the table.



No.	Name	Age.	Sex.	Autopsy.	Biopsy	X-ray.	Ster- nal punct.	W.R.	Bence Jones Prot.	Urine Al- bumen.	Al- bumen G. %.	Glob- ulin G. %.	Fibrin- ogen G. %.	Total Protein G. %.	Serum Calcium mgm. %.	Serum Magnes. mgm. %.	Serum Phosph. mgm. %.	Phos- phatase mgm. %.	Blood Urea mgm. %.	N.P.N. mgm. %.
1	Robt. J.	43	M.	+	-	-	-													
2	Robt. F.	45	M.	+	-	+	-	-ve	Not look- ed for	+					15.4					
3	T. W.	35	M.	+	-	-	-		None found	+					16.2					
4	John S. Mrs	61	M.	+	-	+	-	-ve		None found					9.3		4.4	43.9		
5	Jean F.	48	F.	+	-	+	-	-ve	+	+					9.3					
6	Wm. N.	48	M.	+	-	-	-													
7	Wm. D.	69	M.	+	-	+	+		None found	Trace					10.6, 9.7, 7.3		3.9 4.0	140		
8	Ian C.	55	M.	+	-	+	-			+									58	
9	Geo. F.	86	M.	-	+	+	-													
10	Mrs Janet R.	54	F.	-	+	+	-								10.0					
11	David R.	69	M.	-	+	+	-	-ve												
12	Mrs M.	65	F.	-	+	+	-		+											
13	Robt. G.	65	M.	-	+	+	-	-ve												
14	John B.	28	M.	-	+	+	+	A/C	None found	Trace	2.0 3.13	10.05 10.63			10.4	1.0	3.3	90	11 12	
15	Mrs Isa M.	58	F.	-	+	+	+		+		3.00	2.73	0.30	6.05	9.0		2.5	30	14	36
16	Mrs Mary B.	60	F.	-	-	+	+		++					7.92	8.8		5.3	Normal	60	
17	Robt. F.	56	M.	-	-	+	+	-ve	+	++	2.83 1.53	7.25 5.12	0.73 2.12	10.81 6.77	9.2 8.5		4.0 3.9	71 60	21 18	44 36
18	Chas. E.	50	M.	-	+	+	+	-ve	+		1.98	7.83	0.28	10.09	12.0		3.4 4.1	48 81	23 12	48
19	John W.	42	M.	-	-	+	+				2.58 2.8	3.85 3.98	0.45	6.88 7.06	9 12.7	2.8	4.8 4.0	103 26	20 24	
20	Wm. B.	56	M.	-	-	+	+	-ve	+		2.56	4.12	0.25	6.93	10.0	1.3	2.8	67	27	
21	John H.	63	M.	-	-	+	-	-ve												
22	Helen B.	37	F.	-	-	+	-								15.9		4.9	70		
23	Chas. S.	49	M.	+	-	+	+	-ve							9.8					
24	Mrs M. W.	61	F.	+	+	+	+	-ve	None found											
25	David R.	40	M.	+	+	+	-													
26	Jean R.	33	F.	-	+	+	-	-ve												
27	John C.	17	M.	-	+	+	-		Doubt- ful	+										
28	John E.	52	M.	+	-	-	-	-ve		+										43
29	Sarah S.	58	F.	-	-	+	-		+	+					Normal		Normal			
30	Jas. R.	57	M.	-	-	+	-													
31	Mrs M. S.	52	F.	-	-	+	-	-ve												
32	Mrs Jean N.	67	F.	-	-	+	-													
33	Eliz. B.	56	F.	-	+	+	-		None found						10.7		2.2			
34	Wm. S.	37	M.	+	+	+	-	-ve			2.64	4.53			10.5	1.4	4.3	61	11	
35	Mrs Mary L.	55	F.	-	-	+	-		Absent		4.25	2.00			11.2		4.7	++	45.0	



Cholesterol mgm.%	Creatinine mgm.%	CO <sub>2</sub> Vols.%	Impairment of Kidney	Uric Acid mgm.%	Iron mgm.%	Lactic Acid.	Chlorides (NaCl)	Sugar mgm.%	Sodium mgm.%	Potassium mgm.%	B.S.R. m.m.	1 Hr.	Blood Pressure.	Hemo-globin % Sahli	Colour Index.	Plasma cells in Bld.	Type of Myeloma.	R.B.C.'s in millions	W.B.C.'s	% Myelo-cytes.	% Myelo-blasts.	ADDITIONAL COMMENTS
													145/86	" 26			Plasma celled	2.24	6,600			
													" 37				Plasma celled	2.17	12,900			
													120/80	48	.8		Plasma celled	2.57	6,200			
																	Plasma celled +					+ Not quite typical. Much pus in urine. Amyloid in marrow.
											142		170/100	51	.81		Plasma celled	3.13	9,000			
														33	.8		Plasma celled	2.06	5,600			
180 & 167	1.0	57															Plasma celled	2.75	11,000			
111	1.8	51									150		150/100	50	1.0		Plasma celled	2.48	6,200	+		
	1.0	67		3.3			448	112									Plasma celled				4%	
			+	4.6							10			76	.96		Plasma celled	3.99		+		
115	1.3	68		4.0			520							72 to 86%	.96 to .97		Plasma celled	4.25 to 4.06	6,800 to 4,800			
80	1.2	59		3.2			470				136, 136		118/80	62	.97		Plasma celled	3.18 to 3.10	7,800 to 7,800			
100	2.1	54	+	3.7			460	98			140		180/110	75, 62	1.07		Plasma celled	2.91	6,600	10%	2%	
110	2.10	68		3.4	66	12.5	444	96	327	26	75			60	.99		Plasma celled	3.04	7,400			
122		65			66									68			Plasma celled	3.94	4,200			
100		45		5.0	75		698										Plasma celled	2.45	3,000			
																	Plasma celled					Plasma cell tumour apparently localised to the tonsil.
													120/45	44, 31	.76	46, 59	Plasma celled	2.92	58,000	5.3;	9%	
														50-35%	0.95 to 1.01	31.5% to 39.0%	Plasma celled	2.74 to 1.72	8,200 to 11,600			
														65-85%	1.72 to 1.01	38.0% to 8.0%	Pl. cell Leuk.	4.5-4.1 to -3.69	16,000-10,000-5,800			
																	Myelo-blast.					Myeloblastic type of myeloma.
																	Myelo-blast					" " " "
																						Considered myelomatosis. ? Leukaemic.
	3.5																	4.5	8,200			? Myeloid leukaemia.
													140/80									Radiologically diagnosed as myeloma. Routine exam. of systems (showed nil
													178/108	Haldane's 99%				5.22	9,600			" " " " " " " " " "
																						" " " " " " " " " "
																						Incorrectly diagnosed as myeloma.
160	1.4	61									89			67	0.84			4.03	10,400			At Autopsy found to be carcinoma of bronchus.



Radiology.

In the majority of cases which I have seen and in nearly all those included in my series, where an ante-mortem diagnosis of myeloma has been made, the radiologist has been the first to make a positive suggestion. In every case this should be immediately verified by biopsy. It is thus important to realise that the X-ray appearances are of great value in any given case admitted to hospital with lumbar pain or fracture or any other leading complaint requiring the medical attendant to have an X-ray photograph taken. Yet scant attention is paid to the X-ray findings of myeloma in many well known works on radiological diagnosis. For this reason I have included many photographs of X-rays to show the variety of lesions and the characteristic picture of myeloma, single or multiple. These photographs have in the majority been taken at the Royal Infirmary, Edinburgh, and all have been verified by the radiologist to the hospital, Dr R. McWhirter, to whom I am greatly indebted for much help. Many of the diagnoses were made by him, verified subsequently by biopsy and some by myself by sternal puncture. Some diagnoses have not been verified histologically and are included in a separate group and, though I have no doubt that they are correct, absolute proof is lacking.

In many of the cases the skeleton has been X-rayed/



X-rayed and thus, though frequently autopsy was not available, a very good idea of the extent of the disease is obtained by this method of photography, and it is especially important in that we can appreciate the early lesion anatomically as opposed to the multiple lesion seen in the advanced cases at autopsy. I would therefore like to quote Dr McWhirter's opinion of myelomatosis as a radiologist (This includes out-patients treated in the Infirmary, to which I have no access):

"When first seen many patients have no pain and the first indication of something wrong is the presence of a visible swelling or alternatively they may come to hospital on account of a fracture having taken place. The general health is good and the usual age is over forty, though there have been a few cases in the third decade".

"On examination not infrequently the tumour is a large one and in most cases other than the spine there has been a palpable mass".

"X-ray findings: The main sites of tumour have been in the sternum, pelvis, lumbar spine, ribs, upper ends of femora and skull. There is a radiotranslucent defect with complete absence of reaction in the surrounding bone. As a rule, the lesion is uni-focal, but occasionally there may/

may be more than one area of involvement.

(This is an interesting observation and would indicate that myeloma starts as a single tumour but then the X-ray casts shadows only and many small nodules not yet of sufficient size to attract attention can easily have been overlooked).

Diffuse involvement of the skeleton is not visible in the early stages. Later the skeleton shows the typical appearance associated with multiple myelomatosis. This change may take several years to appear in some of the cases. In none of the cases has there been involvement of the lung fields. This last finding is an important differential point and the diffuse change throughout the skeleton provides corroboration of the diagnosis unless this has been previously established by histological examination".

(An interesting exception to this generalisation is case 8, where the skeleton was X-rayed and beyond some general loss of bone density no indication of myeloma was found. It was subsequently proved by autopsy - Figs. 27-32).

"X-ray Response: With X-ray treatment the

tumour diminishes in size and ultimately disappears and there is some regeneration of/

of the bone in the area affected. As a rule regeneration is not complete. The tumour could be described as moderately radiosensitive. The response is sufficiently good to prevent a fracture taking place and treatment will help a fracture to heal. Treatment would appear to be of very definite value as these patients may live for several years, and, if treated, live this period in reasonable comfort instead of being bedridden".

"After History: In all cases the patient later developed the classical radiological picture of multiple myeloma, these changes appearing within three to four years after the treatment was started".

Dr McWhirter is sure that many cases have been overlooked because the lesions have been regarded as metastatic or they have been referred to as some osteolytic tumour, and in his experience at the Royal Infirmary, Edinburgh, plasmacytoma is more frequent than osteogenic sarcoma, a finding which is quite different to that in most published accounts of bone tumours.

#### Differential Radiological Diagnosis.

The most likely source of confusion was found to be metastatic involvement of the skeleton from carcinoma of the lung. In all cases therefore a photograph/



photograph of the chest should be taken before the diagnosis of plasmacytoma is established. As noted above, plasmacytoma does not involve the lung parenchyma. Photographs of bronchial carcinoma similar to those of multiple myeloma are shown in cases 33 and 34. Case 35, a breast carcinoma with bone metastases, was at first considered myeloma. The primary was very small.

The other disease which causes confusion is reticulum cell sarcoma; when this arises primarily in bone the radiological appearance is very similar to that of plasmacytoma. Again the lesion is purely osteolytic and there is no surrounding bone reaction. These cases may be differentiated often by the enlargement of the superficial lymph glands - a rare finding in myeloma.

References to the radiography of myeloma are comparatively scarce in the literature, and those consulted merely verified the tumour distribution as seen at autopsy. All accentuate the punched out appearance and Geschickter and Copeland say that there is a resemblance to mottling when the multiple areas become confluent. This can be seen in any of the X-rays where the disease is advanced, and at times the differentiation between myeloma and multiple carcinomatosis can be very difficult. More attention should then be paid to the smaller discrete lesions.

Fig. 57 illustrates another difficulty where the/

the tumours of the ribs were so large that they looked like an intrathoracic tumour. This may well lead to a wrong diagnosis, especially if the sternum is so involved and a lateral view must be taken to differentiate from mediastinal tumour.

When looking at the ribs it should be observed that they, when fractured, have not a clean break and the rarefaction is from within. There is no bending as in osteomalacia. The bone erosion from within must be stressed.

The spine may offer difficulties in the early stages of myeloma and a fusiform tumour is not uncommon with apparently no other defects yet visible and also early signs may be localised to vertebral rarefaction and the differentiation between myeloma and localised osteomalacia rendered very difficult. In such a case sternal puncture is imperative as frequently a diagnosis may thus be made even though the sternum may appear normal radiologically. Great rarefaction causing the vertebral bodies to be hour-glass shaped is present in Jacoby's (1930) interesting case of an 8 year old girl.

When the skull is involved the radiographic diagnosis is much easier and there is really no difficulty in deciding between myeloma, Paget's disease, syphilis and leontiasis ossea, as in Paget's disease and leontiasis ossea the bone is thickened and in syphilis the lesion is mottled.

Geschickter/

Geschickter and Copeland stress the enlarged frontal sinuses in some myeloma cases. I have not seen this change.

Coley (1931) in differentiating radiographically between myeloma and giant cell tumour of bone states that myeloma is more in the middle of the bone, whereas giant cell tumour is at the end. This is not my experience, as in myeloma by far the commonest situation of the lesion is at the end of a long bone and especially in humerus and femur at that end nearer to the shoulder and pelvic girdles respectively. Stone (1924) emphasises the trochanteric region of the femur. The punched out appearance and thinning of the cortex are emphasised by Belden (1925) and Whitlock (1924).

Thinning of the cortex can be produced also by a bone cyst, but there is generally some surrounding bone reaction or the cavity may have a loculated appearance and the margin is seldom so definite. Myeloma, however, especially when large, can have a cystic appearance.

More difficulty is experienced in rare forms of granuloma, according to Altschul (1926), who finds that sporotrichosis can also call forth similar pictures, and in a case of Hand Schuller Christian disease seen by me recently the lesion in the skull could easily be confused with myeloma.

The/



The radiologist then often is the first to suggest a definite diagnosis and a study of the radiological lesion is of the very greatest importance, but in view of the diseases giving similar pictures, verification by biopsy or sternal puncture is essential.

### The Diagnosis of Myeloma.

In the older records doubtless the diagnosis of myeloma was made occasionally by careful examination of the urine and the discovery therein of Bence-Jones protein. Frequently the pathologist was the first to point out the nature of the disease. The clinician was usually able to make the diagnosis only when the disease was advanced. The everyday use of X-ray photography has altered all this, particularly in institutions where a plant is at hand. In the cases published in the literature of recent years and in the series of cases in this thesis one is impressed by how often a fracture or low back pain is the first indication of the pathological process. When such accidents occur these days, immediately the site of fracture or pain is X-rayed and at least a suggestion, if not a correct impression, of the disease process is made by the radiologist, who therefore holds an important position in the forming of the diagnosis in myeloma. However good may be the radiologist's opinion, it has to be verified. Two methods of verification are open to the clinician - biopsy and sternal puncture. The former is more elaborate, painful and time consuming, the latter is simple and quick, and also it is 80% accurate; the choice of tissue for biopsy may be difficult to make. There is little doubt that with the facilities of modern medicine/

medicine a diagnosis of myeloma should not be difficult to make, and the combination of X-ray photography and sternal puncture is adequate in the vast majority of cases. I consider that the estimations of phosphatase, serum calcium and phosphorus, the blood sedimentation rate and the appearance of Bence-Jones protein are interesting academic accessories; they are not essential for a plain diagnosis.

It is because of the important part played by the radiologist that I have appended representative photographs. In the cases which I have seen the diagnosis of myeloma was not made before an X-ray photograph was taken, and unless clinician and radiologist are aware of the appearance of a myeloma in an X-ray a verifying sternal puncture would not be contemplated. I would stress then the great importance of radiology to myeloma diagnosis.

Frequently the X-ray picture of myeloma is either not recognised or is not quite typical and the common misdiagnoses are, so far as the radiologist is concerned, osteitis fibrosa cystica, generalised and local, giant cell tumour of bone, osteomyelitis, osteomalacia and metastatic carcinoma. More rarely an erroneous diagnosis of sarcoma, Ewing's tumour, neuroblastoma, chloroma and one or other of the Xanthomatoses, such as Hand Schuller Christian or Gaucher disease, is made. Paget's disease of bone and/



and tuberculosis apparently have not caused much difficulty in the differential diagnosis.

From the radiology point of view, in my series of cases confusion was most frequent between myeloma and generalised osteitis fibrosa cystica (hyperparathyroidism), giant cell tumour or metastatic carcinoma.

In other cases where X-ray photography was not used diagnoses of leukaemia, with or without chloroma, nephritis, transverse myelitis and trauma (vertebral collapse) have been made. In my series all these possibilities were at least once mentioned. The diagnosis of nephritis is interesting; the presence of Bence-Jones protein in the urine was so abundant, though not recognised as such, that kidney disease was thought to be present.

Hodgkin's disease and lymphosarcoma were also mentioned as possibilities in the literature.

Other possibilities have been mentioned, but they were wild suggestions.

In summary the X-ray picture and the sternal bone marrow picture, each of which have been described above, is the most effective method of establishing a diagnosis after a careful history has been taken. Biochemical findings are only corroborative so far as the diagnosis is concerned.

### Prognosis

The ultimate prognosis in multiple myeloma is invariably bad. The immediate prognosis depends on the stage of the disease when diagnosed. If an early diagnosis is made the patient may be able to live a useful and comfortable life for months or years and with the help of X-ray therapy a few months will be added to the life. Generally the diagnosis is not early and death usually occurs in two years from when the diagnosis was made. With X-ray treatment there is no doubt that life is lengthened but in the end the disease runs its course. There are some cases in the literature, already quoted, which have lived for 8 or 10 years. These are exceptional but they are not cured. The disease always recurs and in the terminal stages X-rays have no effect.

In the solitary myeloma the ultimate prognosis is equally bad though the course of the disease may be longer and the immediate prognosis less serious. The extra-medullary type, however, has a good prognosis if surgical treatment is started at once. Provided excision has been complete it does not recur in the vast majority of cases.

Treatment/

### Treatment

This is most unsatisfactory. Excision, out scraping/the bone, amputation and Coley's fluid have all been tried and various claims made. Any local treatment is bound to fail in the multiple form, it stands to reason. The so-called solitary form will only benefit temporarily, but it is hardly ever justifiable to amputate. Excision, scraping out the bone and Coley's fluid are merely palliative and from the purely therapeutical point of view useless.

X-ray treatment is by far the most successful. Fractures will heal with the help of X-rays and temporarily the patient's general comfort is enormously increased. The disease, however, always returns.

Excision of the extra-medullary type is successful. I have no experience of the effect of X-rays on these myelomata.



GENERAL SUMMARY

1. The myeloma is defined, a short history of the disease is given and the possibility of different types discussed.
2. Reports of 29 cases of myeloma are given and 3 misdiagnosed cases, 2 cases of chloroma and 1 case of plasma cell leukaemia.
3. The relationship between the malignant cell of myeloma (the myeloma cell) and the plasma cell is discussed; a short history of the plasma cell and a description is given; the myeloma cell and the plasma cell are compared.
4. The myeloma cell and the plasma cell are considered to be quite different and for this reason the name plasmacytoma is discouraged.
5. The myeloma cell is probably a malignant haemocyto blast and the name haemocyto blastoma is suggested for the tumour.
6. The myeloma is mainly a disease of bone marrow, and is confined to bone marrow, but metastases to the viscera may occur and tumours of this type outside the skeletal system are recognised.
7. The association between myeloma and leukaemia is discussed with special reference to plasma cell leukaemia.

8. The biochemical findings in cases of myeloma are described, with particular attention paid to the plasma proteins. The meaning of hyper-proteinaemia in myelomatosis is discussed and the association between this phenomenon and Bence-Jones proteinuria and the blood sedimentation rate is discussed.
9. The association between serum proteins and amyloid is described.
10. The importance of X-ray photography in recognising the pathological process is stressed and the necessity of verification by sternal puncture is stressed.
11. The interpretation of the differential count in bone marrow smears is discussed and a method of puncturing the sternum is described.
12. Prognosis is poor in the multiple myelomatosis and so-called solitary myeloma, but good in the extra-medullary type.
13. Treatment is unsatisfactory. X-rays, however, do give the patient a longer lease of life but they are not curative.

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Dr McWhirter of the Royal Infirmary has shown me all the available X-ray plates of myelomata seen at the Infirmary and allowed me to use copies in this thesis.

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Dr J.C. Tainsh of the Royal Northern Infirmary, Inverness, sent me the X-ray plates of Cases No. 16 and No. 35.

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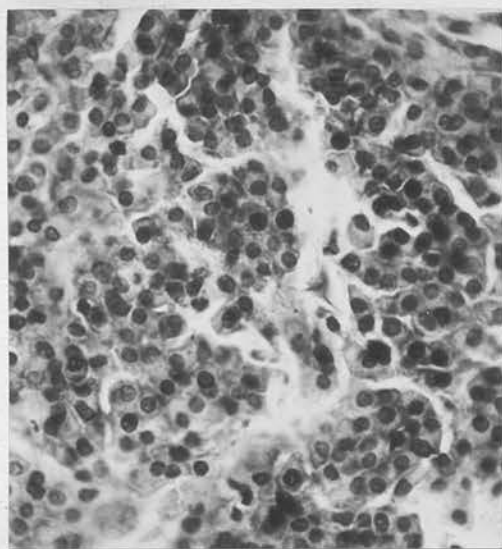
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Fig. 1. Section from tumour of sacrum. Plasmacytoma.  
x 380. H.E.

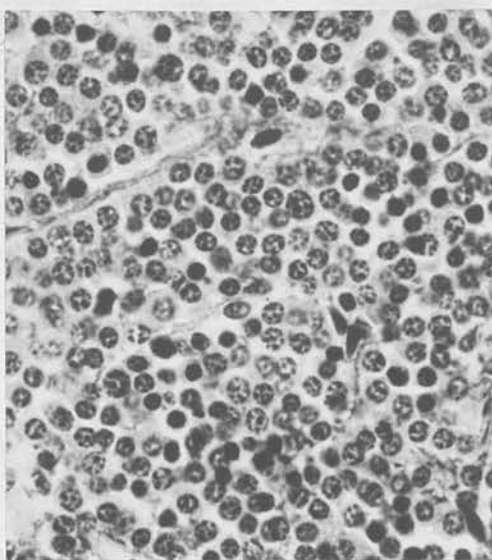
Fig. 2. Section of bone marrow invaded by tumour,  
showing plasmacytoma cells. The typical  
peripheral angular chromatin blocks are  
clear. x 380. Heidenhain's iron  
haematoxylin.

Fig. 3. Section of 5th dorsal vertebra showing  
nodular myeloma growths. The sur-  
rounding bone marrow and bone  
trabeculae are normal. x 7. H.E.

Fig. 4. Section of 6th dorsal vertebra where the  
myeloma nodules have coalesced and the  
bone structure has collapsed. There  
is no normal marrow. x 7. E.M.B.



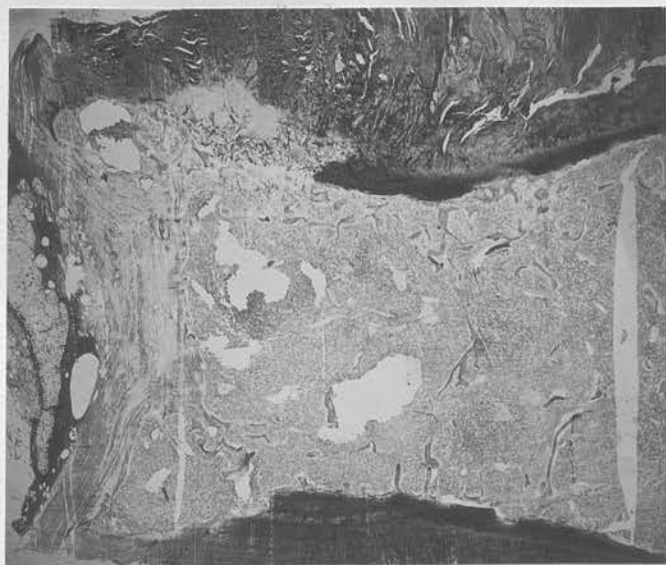
Case I, Fig. 1 x 350.



Case II, Fig. 2 x 350.



Case II, Fig. 3 x 7.



Case II, Fig. 4 x 7.



Fig. 5. X-ray of masserated specimen of vertebral column.

There is marked decalcification and vertebral collapse.

Fig. 6. Vertebral column. Due to the softened bone the vertebrae have collapsed and the inter-vertebral discs have expanded with the production of little herniations into the bone (c.f. Fig. 5). The sternum is entirely infiltrated and there are cavities in the manubrium.

Fig. 7. Section of a tumour mass. The cells are typical of the plasmacytoma. The paranuclear clear area is well marked, and there is an absence of supporting tissue. x 320. H.E.

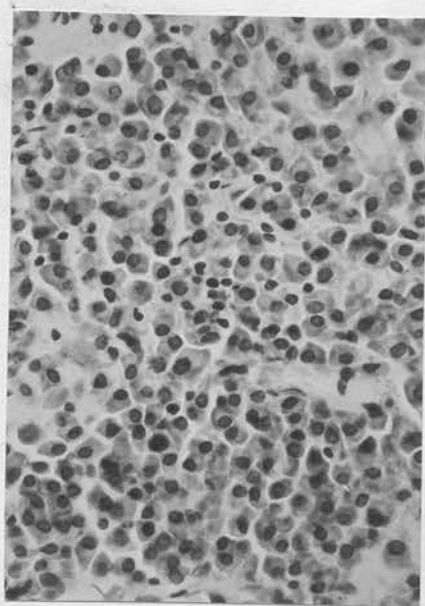
Fig. 8. X-ray of skull showing minute nodules of myeloma in large numbers. This condition was at first thought to be osteitis fibrosa cystica. c.f. Fig. 11.



Case III, Fig. 5.



Case III, Fig. 6.



Case IV, Fig. 7 x 320.



Case IV, Fig. 8.

Opposite p. 247.

Fig. 9. Lumbar vertebrae. Rarefaction of bone and compression of the bodies.

Fig. 10. Right humerus. Myeloma of the head causing fracture of the surgical neck. There are three small nodules in the proximal part of the shaft.

Fig. 11. Calvarium, showing many minute myeloma nodules (c.f. Fig. 8). They are bilateral and discrete.

Fig. 12. Right innominate bone and head of femur, both heavily infiltrated by myeloma.

Fig. 13. Left innominate bone with large tumour and multiple nodules in the walls of the acetabulum.

Fig. 14. Right and left femora. Proximal half in each bone affected.





Case V, Fig. 10.

Case V, Fig. 9.



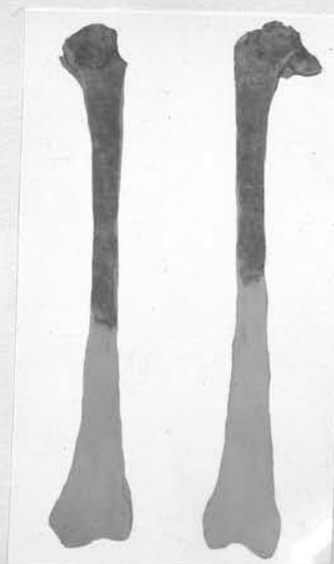
Case V, Fig. 11.



Case V, Fig. 12.



Case V, Fig. 13.



Case V, Fig. 14.

Opposite p. 248.

Fig. 15. Lumbar vertebrae. Bodies and spines entirely myelomatous. The bodies have collapsed and there is expansion of the nucleus pulposus.

Fig. 16. Section of Kidney showing casts, possibly of Bence-Jones protein, surrounded by renal epithelial cells which have been shed from further up the tubule. x 350. H.E.

Fig. 17. Section of Kidney. There is fibrosis and the casts are surrounded by what look like giant cells. The origin of this fibrosis is probably mixed arterial and parenchymatous. It is possible that the presence of these casts have increased the fibrosis. x 200. H.E.

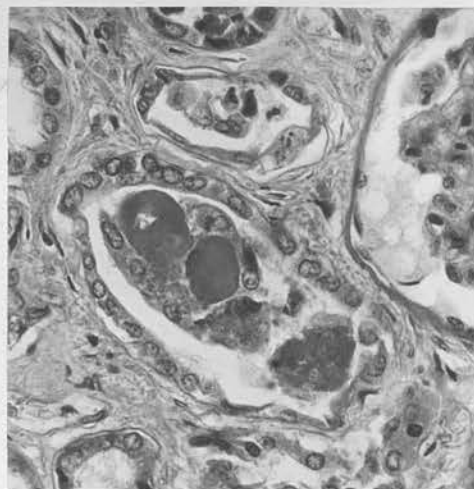
Fig. 18. Section of Kidney showing the early formation of giant cells. The adherent cells seem to be attempting to phagocytose the cast. x 350. H.E.

Fig. 19. Section of Spleen. There are many cells in the sinusoids indistinguishable from the myeloma cells of the tumour. No blood film available. x 400. H.E.

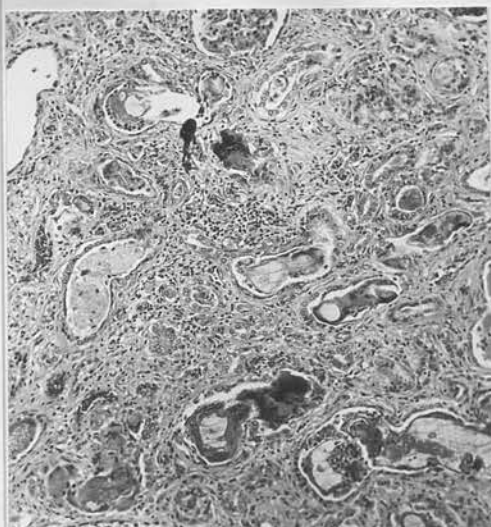
Fig. 20. Autopsy section of bone marrow. The angular blocks of chromatin are not quite so typical as the paranuclear clear area is less marked than in the usual plasmacytoma. The central nucleolus is generally well marked. Heidenhain's iron-haematoxylin. x 500.



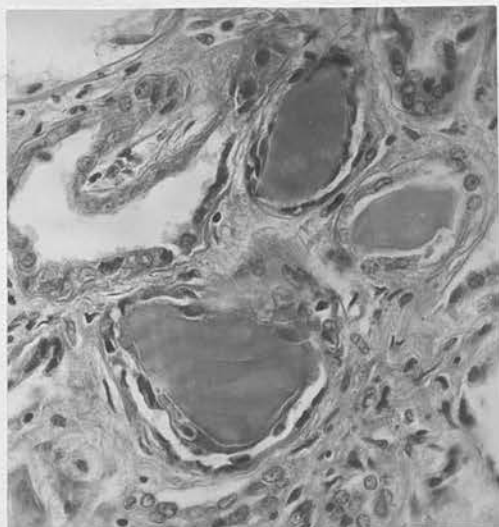
Case V, Fig. 15.



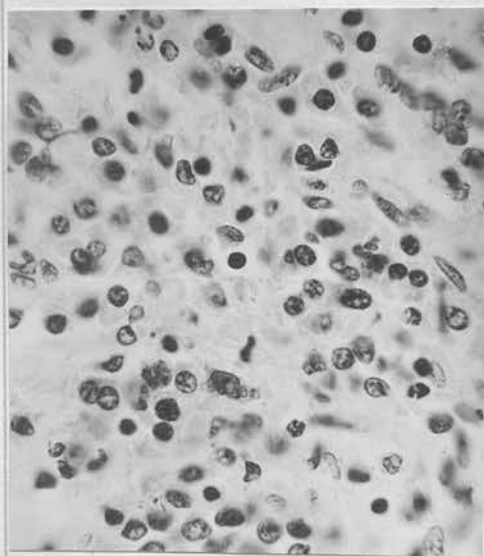
Case V, Fig. 16. x 350.



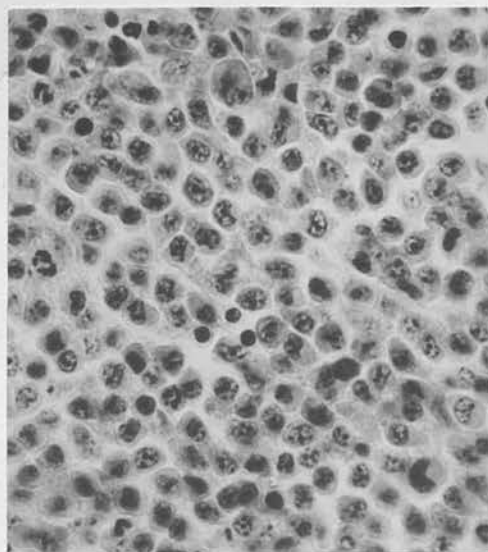
Case V, Fig. 17 x 200.



Case V, Fig. 18 x 350.



Case V, Fig. 19 x 400.



Case VI, Fig. 20 x 500.



Opposite p. 249.

Fig. 21. Autopsy section of bone marrow. Amyloid degeneration. x 18. Congo red.

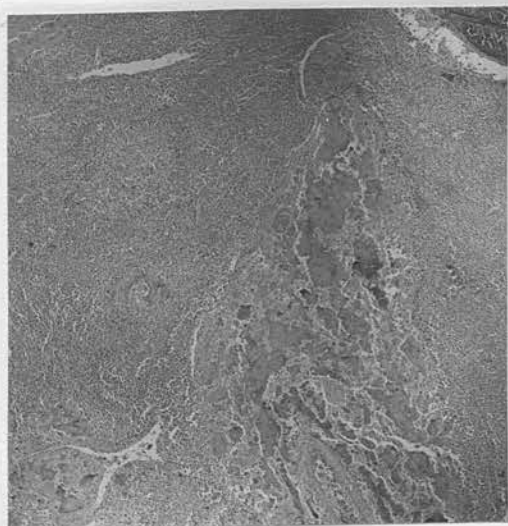
Fig. 22. Autopsy section of bone marrow. The cytoplasmic clear area is seen and also the nucleolus. There is one binucleated cell. x 650. H.E.

Fig. 23. Pituitary Gland. Infarction of almost entire posterior lobe. x 7. H.E.

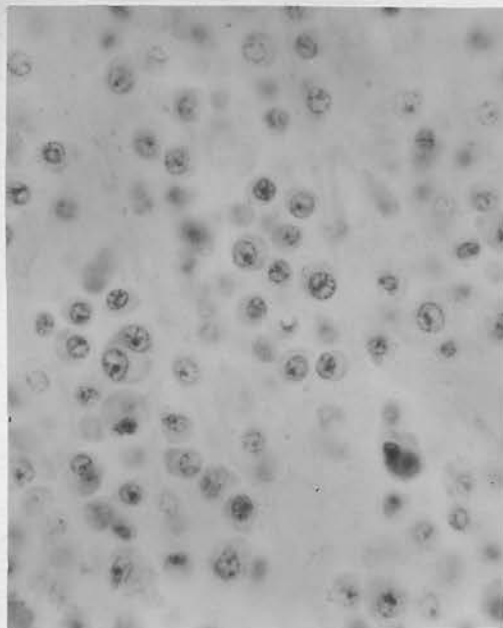
Fig. 24. Section of Spleen. Cells indistinguishable from myeloma cells in the sinusoids. x 900. H.E.

Fig. 25. Section of Femur Marrow. There is early autolysis. The cells, however, can be seen to be plasmacytomatous. x 400. H.E.

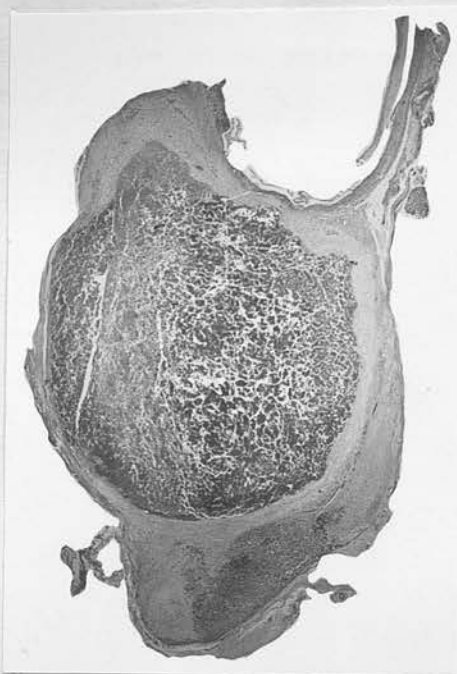
Fig. 26. Section of Spleen. Much myeloid metaplasia present. The cells are mainly haemocyto blasts and primitive normoblasts.



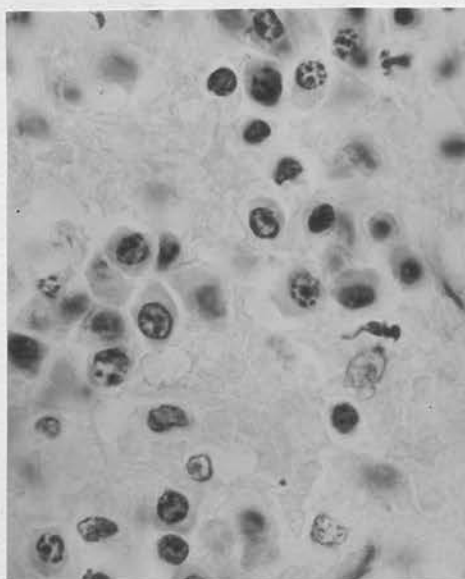
Case VI, Fig. 21 x 18.



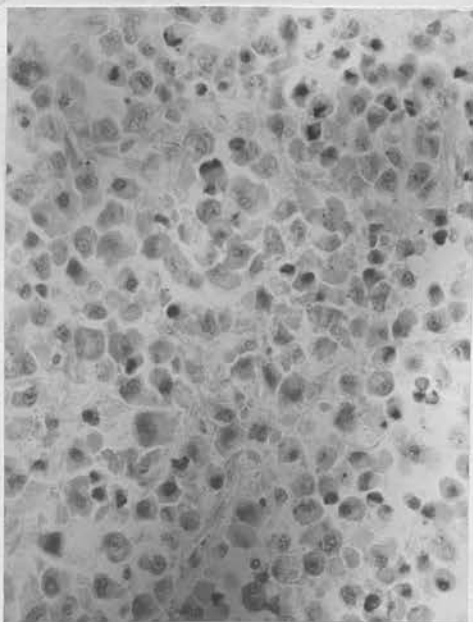
Case VII, Fig. 22 x 650.



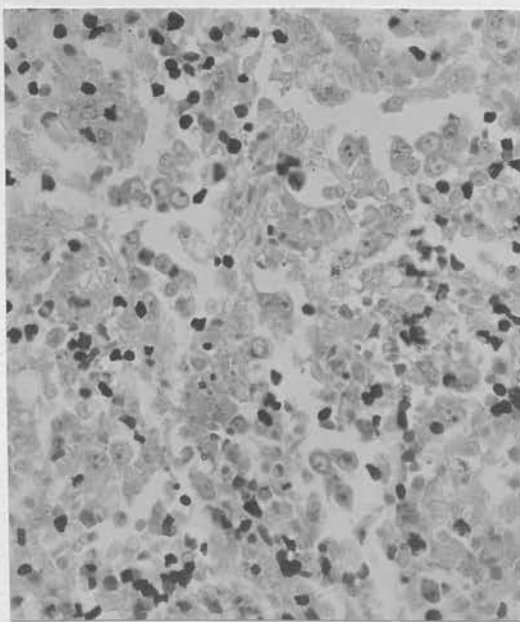
Case VII, Fig. 23 x 7.



Case VII, Fig. 24 x 900.



Case VIII, Fig. 25 x 400

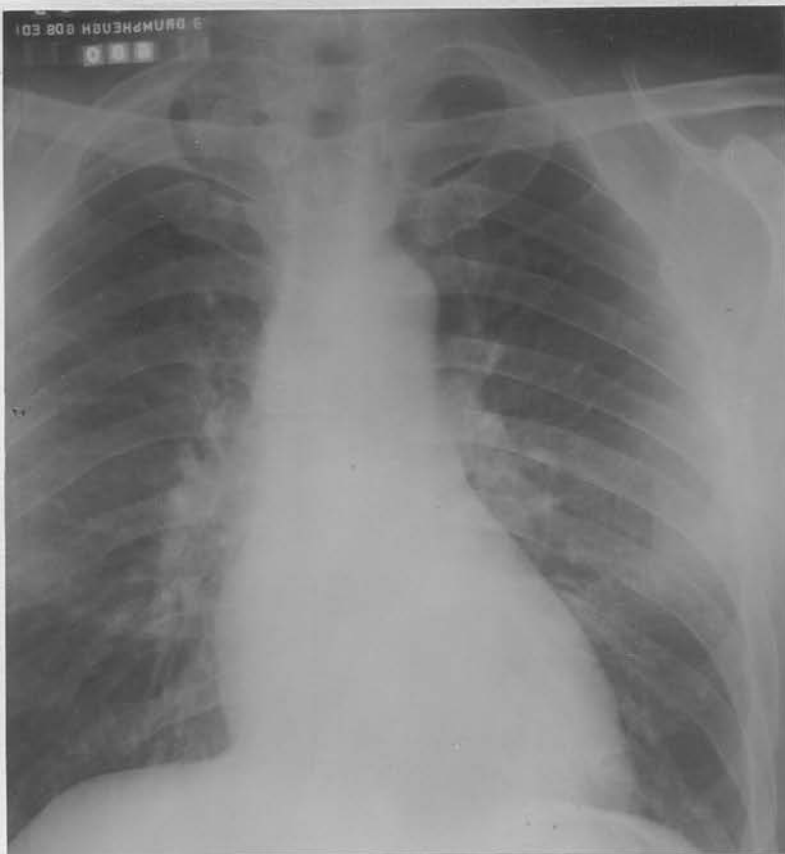


Case VIII, Fig. 26 x 350

Opposite p. 250.

Figs. 27 - 32: X-rays of thorax, pelvis and vertebral column. There is no sign of myelomatosis which, however, was found to be widespread at autopsy. These photographs demonstrate that X-rays can be negative, though very rarely, in myelomatosis. There is slight porosis.





Case VIII, Fig. 27.



Case VIII, Fig. 28.



Case VIII, Fig. 29.



Case VIII, Fig. 30.



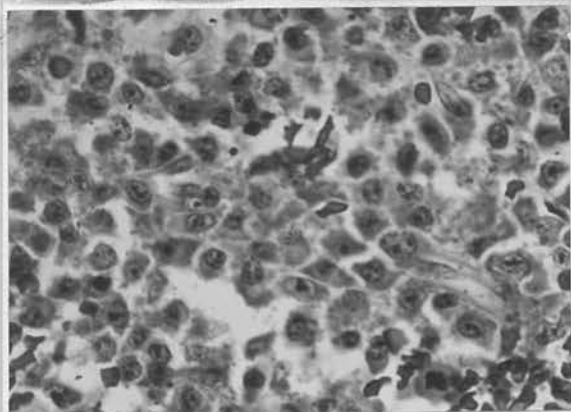
Case VIII, Fig. 31.



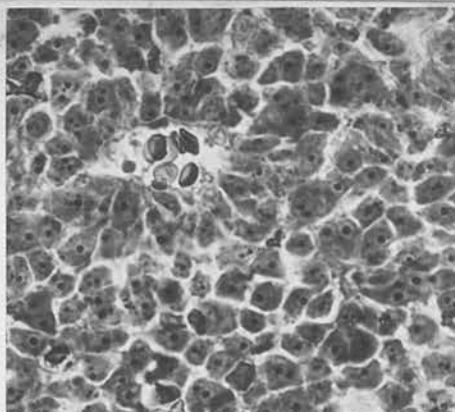
Case VIII, Fig. 32.

- Fig. 33. Section of upper jaw - biopsy. Plasma-cytoma with poor supporting tissue. x 500. H.E.
- Fig. 34. Section of manubrium - biopsy. Plasma-cytoma. The eccentric nucleus and prominent nucleolus are clearly seen. x 500. E.M.B.
- Fig. 35. Section of bony tumour - biopsy. Plasma-cytoma. Many cells show the angular blocks of chromatin so characteristic of plasma cells. x 500. Heidenhain's iron haematoxylin.
- Fig. 36. Section of sternum - biopsy. Plasma-cytoma. Binucleated cells and prominent nucleoli are clear. The cytoplasm is amphophilic. The "hof" is not so clear as usual. x 500. H.E.
- Fig. 37. Section frontal bone - biopsy. Plasma-cytoma. The highly cellular appearance of the tumour is well shown. x 500. H.E.
- Fig. 38. Section from Femur - biopsy. Plasmacytoma. The photograph is a little over exposed, but it shows the granular cytoplasm. The cells are fairly large. The "hof" can be seen and the nucleolus in an eccentric nucleus. x 500. H.E.
- Fig. 39. Sternal puncture. Bone Marrow. General view showing only two myeloma cells in the upper middle part of the field and two less distinctly in the lower middle field. They are marked by arrows. x 500. Leishman.
- Fig. 40. Same film as Fig. 39. Higher power. Myeloma cells marked by arrows. The nuclei are not distinctive in the photograph of this preparation.
- Fig. 40a. Same marrow as in Fig. 39. Thick smear. The myeloma cells are quite definitely peroxidase negative. Promyelocytes are shown as comparison. x 900.

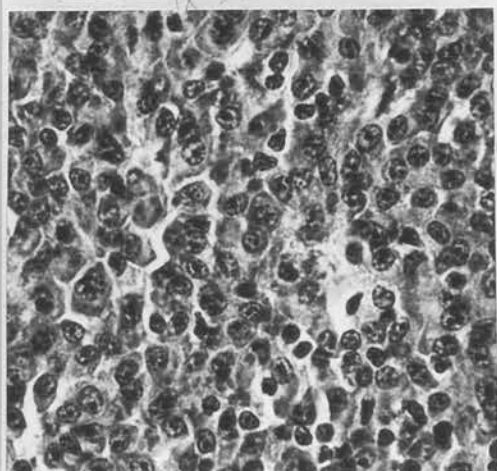




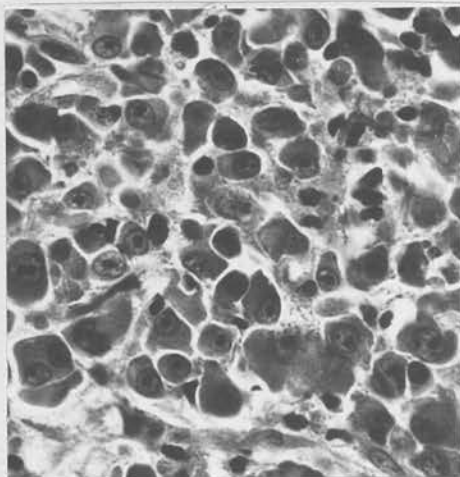
Case IX, Fig. 33 x 500.



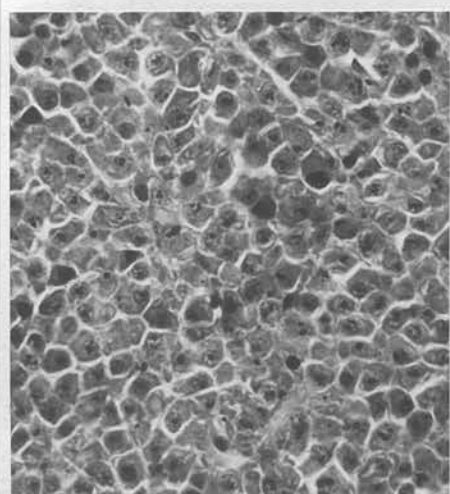
Case XI, Fig. 34 x 500.



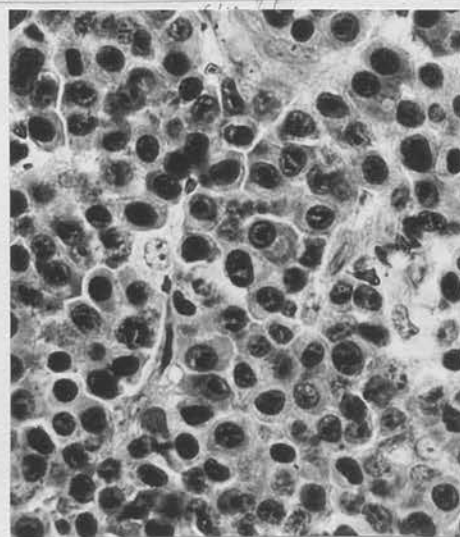
Case XII, Fig. 35 x 500.



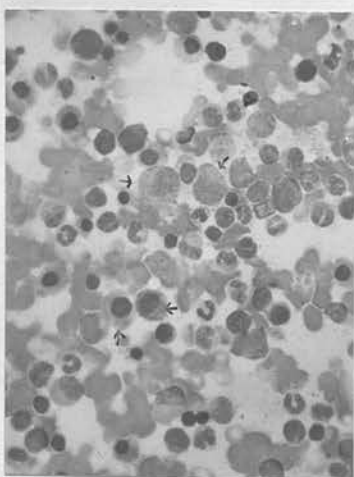
Case XIII, Fig. 36 x 500.



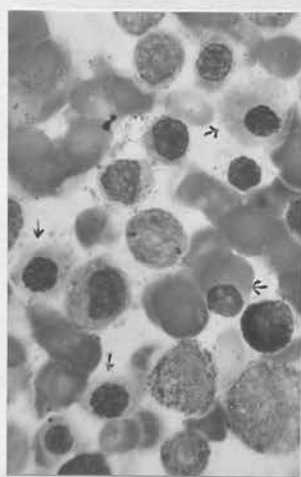
Case XIV, Fig. 37 x 500.



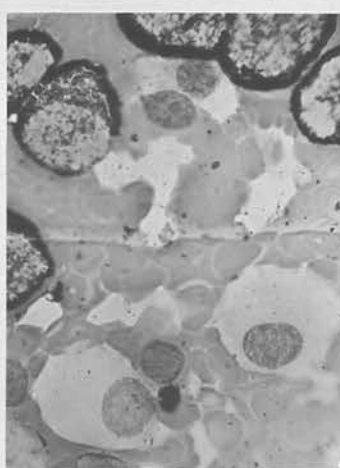
Case XV, Fig. 38 x 500.



Case XV, Fig. 39 x 500



Case XV, Fig. 40.



Case XV, Fig. 40a x 900

Opposite p. 253.

Figs. 41 & 42: Antero-posterior and lateral views of dorsal vertebrae, showing erosion of 5th and collapse of 8th dorsal vertebrae.

Fig. 43: X-ray of skull. Small areas of bony change. They are very difficult to see in the frontal bone but are frequent there. At first thought to be carcinoma deposits, subsequently proved to be due to myelomatosis.

Figs. 44 & 45: X-ray photographs showing a myelomatous tumour of the manubrium sterni before X-ray therapy and in the early stages of therapy. The soft tissue swelling is clear and it actually increased in size after the first dose of X-rays; the compact bone broke down.



Case X, Fig. 41.



Case X, Fig. 42.



Case X, Fig. 43.



Case XI, Fig. 44.



Case XI, Fig. 45.



Opposite p. 254.

Fig. 46: The same case as Fig. 44 after X-ray therapy. The manubrium is fairly well reconstructed, though osteoporotic, and the soft tissue swelling has disappeared.

Fig. 47: Slightly oblique view of thorax, same case as Fig. 44. The expanse of the manubrial tumour is shown and a few myeloma nodules are seen in the ribs. There is also osteoporosis.



Case XI, Fig. 46.



Case XI, Fig. 47.

Opposite p. 255.

Fig. 48: X-ray of pelvis, showing sclerosis of the bone. This is unusual in myeloma.

Figs. 49 & 50: Antero-posterior and lateral views of thoracic vertebrae showing generalised decalcification and anterior collapse of the 10th dorsal vertebra.





Case XI, Fig. 48.



Case XII, Fig. 49.



Case XII, Fig. 50.

Opposite p. 256.

Figs. 51 & 52: Same case as Fig. 49, 18 months later.

The 9th dorsal vertebra is now collapsing and there is some recalcification of both.

Fig. 53: X-ray of left shoulder, showing multiple foci in the acromion process, scapula and head of humerus. The ribs are normal. The humerus has a kind of greenstick pathological fracture.



Case XII, Fig. 51.



Case XII, Fig. 52.



Case XII, Fig. 53.



Opposite p. 257.

Fig. 54: X-ray skull. Widespread foci in the calvarium.

Fig. 55: X-ray of thoracic spine. The 9th and 10th dorsal vertebrae show satisfactory calcification and the condition is quiescent. This is a result of X-ray therapy.

Fig. 56: X-ray of right femur. Plasmacytoma, showing typical erosion from within and cyst-like appearance. There is no bone reaction. Note the calcified arteries. The sternum was also affected in this case. The tumours responded well to X-ray therapy.



Case XII, Fig. 54.



Case XII, Fig. 55.



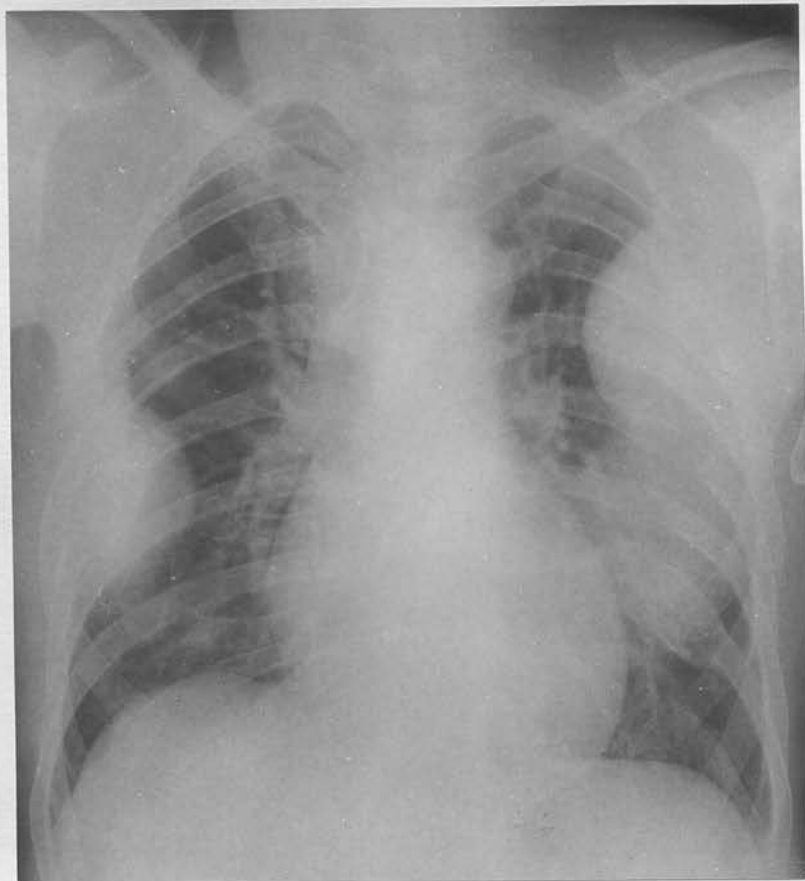
Case XIII, Fig. 56.

Opposite p. 258.

Fig. 57: X-ray of thorax showing several areas of rib destruction with large rib tumours protruding into the chest. These tumours are NOT in the lungs.

Fig. 58: X-ray of pelvis. Gross bone destruction in ischia, ilia and left pubic bone.





Case XIV, Fig. 57.



Case XIV, Fig. 58.

Opposite p. 259.

Figs. 59 & 60: X-ray of skull. Areas of bone  
destruction in the frontal bones  
and single areas in the parietal  
and occipital bones.



Case XIV, Fig. 59.



Case XIV, Fig. 60.



Opposite p. 260.

Figs. 61-63: X-ray of right femur. Fracture of the mid-shaft of the bone through a myeloma. The callous formation is shown to progress favourably. Photographs taken at intervals of approximately one month.

Fig. 64: Same bone as in Fig. 61. Bad apposition, but there is bony union with several small myelomata in the shaft. Taken 3 months after Fig. 63, and at the same time as Fig. 65.

Fig. 65: X-ray right humerus. Gross destruction of bone, a gap of 4 inches, due to myeloma. Notice the rarefaction of bone.

Fig. 66: X-ray of right tibia and fibula. There are many small radiotranslucent areas.



Case XV, Fig. 61

Case XV, Fig. 62

Case XV, Fig. 64

Case XV, Fig. 63



Case XV, Fig. 65.



Case XV, Fig. 66.

Opposite p. 261.

Fig. 67: X-ray of pelvis. Rarefaction of pelvic bones in general. Erosion of right pubic bone near symphysis.

Fig. 68: Sternal puncture. Bone marrow. Thick smear showing the myeloma cells of plasmacytoma. Note the clear area and "granuloplasm". x 800. Leishman.

Fig. 69: Sternal puncture. Bone marrow. Low power view. The typical myeloma cells of plasmacytoma compared to myelocytes, leucocytes and late normoblasts. One myeloma cell is in mitosis. x 300. Leishman.

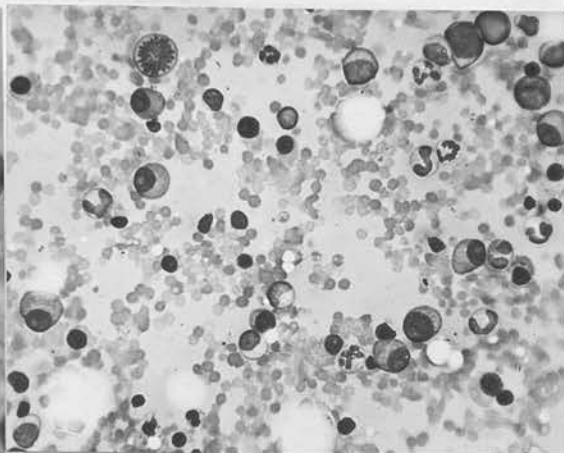
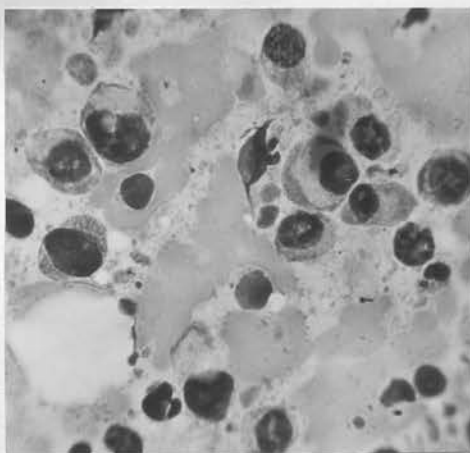
Figs. 70 & 71: Higher power of myeloma cells; same case as Fig. 69. The large spherical cell with eccentric nucleus and central nucleolus is diagnostic of this type of myeloma cell. Two myelocytes are in the field as comparison. The "hof" is often not distinctive and, as here, may look like a light smudge. The granular cytoplasm is typical. Multi-nucleated cells are commonly seen. The giant cell in Fig. 71 has at least 3 nuclei, probably 4. x 900 & 750. Leishman.

Fig. 72: Same case as Fig. 69. The myeloma cells are peroxidase negative. x 400.



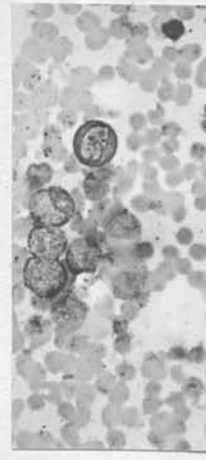
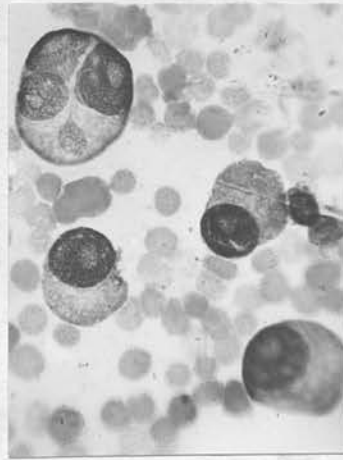
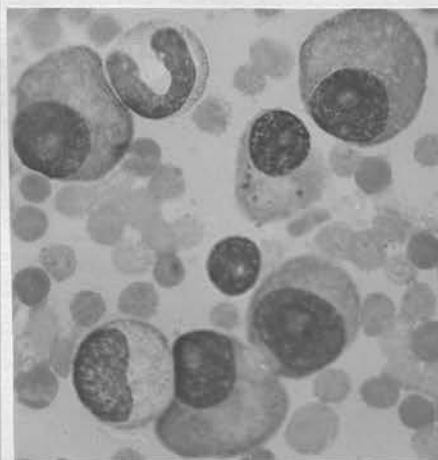


Case XV, Fig. 67.



Case XVI, Fig. 68 x 800

Case XVII, Fig. 69 x 300.



Case XVII, Fig. 70 x 900

Case XVII, Fig. 72 x 400

Case XVII, Fig. 71 x 750

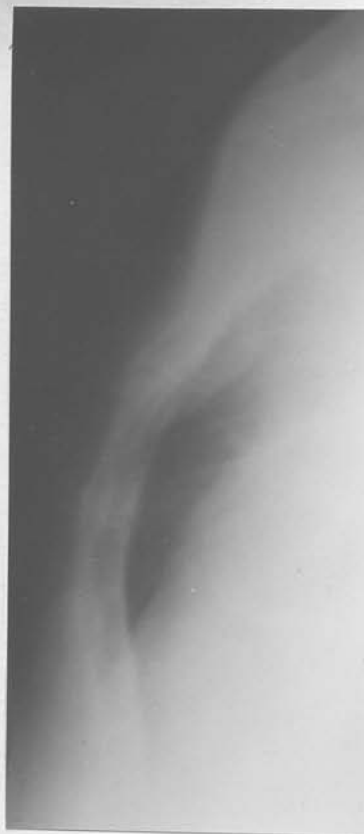
Opposite p. 262.

Figs. 73 & 75: X-ray photographs of skull showing multiple discrete, punched out, circular areas of decalcification without bony reaction, so typical of multiple myelomatosis.

Fig. 74: X-ray of sternum. The bone is decalcified and the manubrium is swollen.



Case XVI, Fig. 73.



Case XVI, Fig. 74.



Case XVI, Fig. 75.



Opposite p. 263.

Figs. 76 & 77: X-rays of left and right shoulder regions showing gross bony changes in all the ribs, both scapulae, both clavicles and both humeri. There is no fracture evident yet. These photographs show the extraordinary extent of bony change which may occur in multiple myelomatosis.

Fig. 78: X-ray showing lower cervical and upper dorsal vertebrae all of which have myeloma nodules. Clavicles, sternum and scapulae are also affected.

Figs. 79 & 80: X-rays of right and left tibiae and fibulae. Very small, discrete, translucent areas in the shaft of the bones. In Fig. 79 they have to be looked for carefully.



Case XVI, Fig. 76.



Case XVI, Fig. 79.



Case XVI, Fig. 77.



Case XVI, Fig. 78.



Case XVI, Fig. 80.

Opposite p. 264.

Figs. 81 - 84: X-rays of the vertebral column showing  
decalcification and extensive  
myelomatosis. There is some collapse  
of the 8th dorsal vertebra.





Case XVI, Fig. 81.



Case XVI, Fig. 82.



Case XVI, Fig. 83.



Case XVI, Fig. 84.

Opposite p. 265.

Fig. 85: X-ray of pelvis. Involvement of all the pelvic bones. Multiple little translucent areas are especially clearly seen in pubic bones.

Figs. 86 & 87: X-rays of right and left femoral shafts showing the discrete areas of myelomata.

Figs. 73 - 87 should be studied as a whole, as they demonstrate the enormous extent to which the skeleton may be damaged in myelomatosis and yet the only positive finding clinically was a thickened right clavicle. Later Bence-Jones protein was found in the urine, but the blood sedimentation rate was only 10 mm/hour. To estimate the extent of the disease on clinical grounds alone is then wholly inaccurate, probably in all cases.



Case XVI, Fig. 85.



Case XVI, Fig. 86.



Case XVI, Fig. 87.

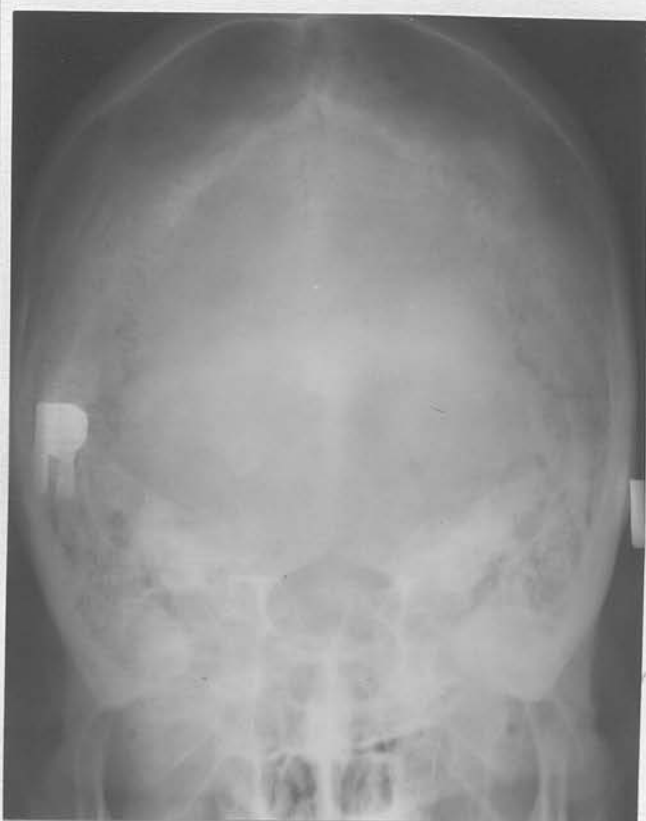


Figs. 88 & 89: X-rays of skull. The calvarium is normal. There is destruction of the apex of the right petrous temporal bone, the dorsum sellae and an area in the left lower frontal region.

Fig. 90: X-ray of left humerus. There are numerous small myelomata in the medulla of the bone, but they are not distinct in this reproduction.



Case XVII, Fig. 88.



Case XVII, Fig. 89.



Case XVII, Fig. 90

Opposite p. 267.

Figs. 91 & 92: X-rays of right and left femora.

Both show myelomata. The erosion of the compact bone from within in Fig. 91 is typical. This is the kind of lesion that gives reason for a fracture and diagnosis of solitary myeloma, unless the entire skeleton is photographed.

Fig. 93: X-ray of thoracic spine. Typical appearance of myelomatosis but no vertebral collapse yet. Nearly all the vertebrae are affected.

Fig. 94: X-ray of right humerus. Faint translucency of extensive multiple lesions.





Case XVII, Fig. 91



Case XVII, Fig. 92



Case XVII, Fig. 93



Case XVII, Fig. 94

Opposite p. 268.

Fig. 95: X-ray of pelvis. Large area of rarefaction in the left pubo-ischial ramus.

Figs. 96 & 97: X-rays of lumbar spine. The 1st lumbar vertebra has a compression fracture and there is flattening of the 5th. The texture of the bone of the 1st lumbar vertebra is not quite typical of myeloma. The vertebrae in general are decalcified and the expansion of the nucleus pulposus is very clearly shown.



Case XVII, Fig. 95.



Case XVII, Fig. 96.



Case XVII, Fig. 97.



Opposite p. 269.

Fig. 98: X-ray of thorax. The ribs are rarefied. There are large lesions in 4th left rib and 9th right rib. The former lesion is not clear in this reproduction.

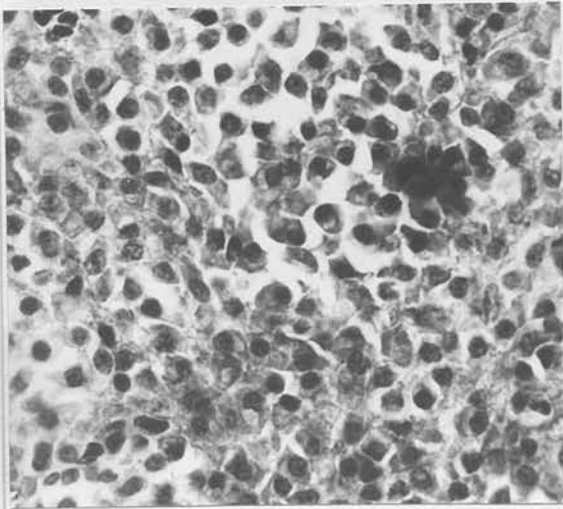
Figs. 88-98: These should be examined as a whole as they show the varied extent of the lesion.

Fig. 99: Biopsy right iliac bone. Typical plasma-cytoma. The preparation is not particularly good but the essential features so typical of the myeloma cell can be recognised. (c.f. Fig. 100). x 500. H.E.

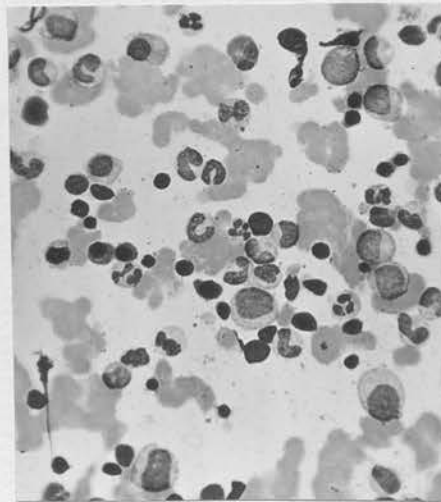
Fig. 100: Sternal puncture. Bone marrow. Showing 6 myeloma cells. Same case as Fig. 99. This brings out the difference between the paraffin and smear appearances of these malignant cells. They look very different and the paraffin section malignant cell can be much more favourably compared to a plasma cell than those cells seen in the smear. Also notice the low count of myeloma cells in the smear in quite an advanced case.



Case XVII, Fig. 98.



Case XVIII, Fig. 99 x 500.



Case XVIII, Fig. 100 x 350.

Opposite p. 270.

Fig. 101: X-ray of skull. Multiple areas of rarefaction throughout skull and jaw.

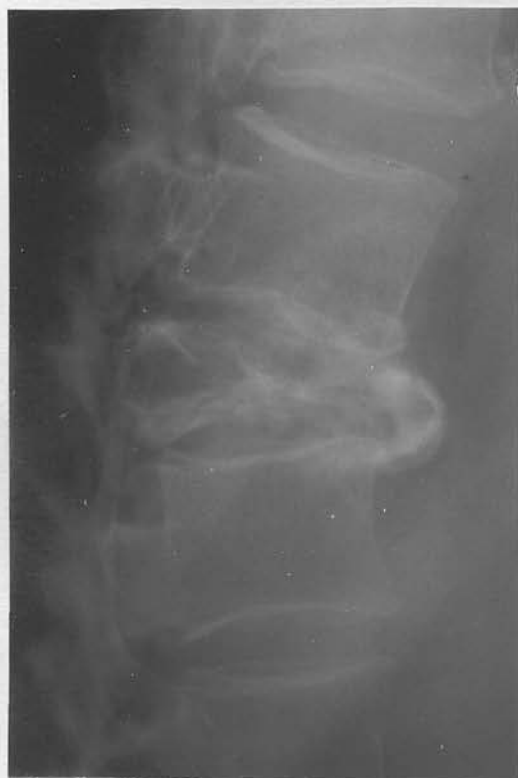
Fig. 102: X-ray of lumbar spine. Collapse of 2nd lumbar vertebra. This was at first thought to be a giant cell tumour.

Fig. 103: X-ray of right iliac bone. Cystic tumour at the crest and smaller tumours underneath. From this region a biopsy was taken.





Case XVIII, Fig. 101.



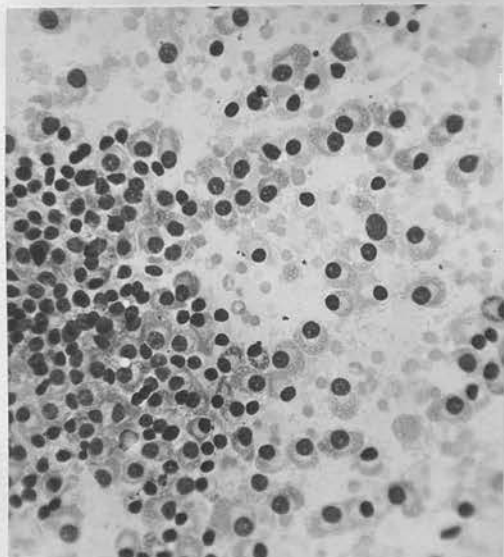
Case XVIII, Fig. 102.



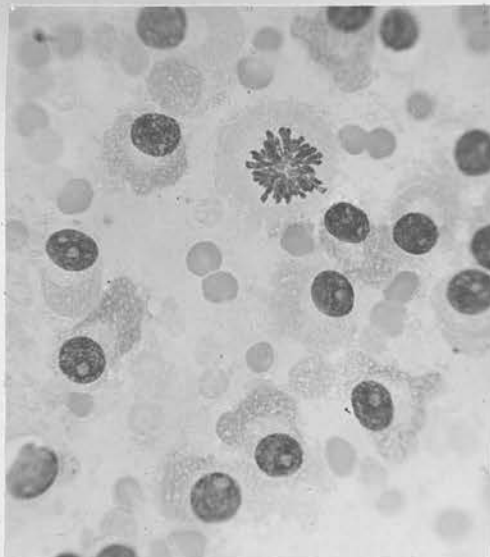
Case XVIII, Fig. 103.

Opposite p. 271.

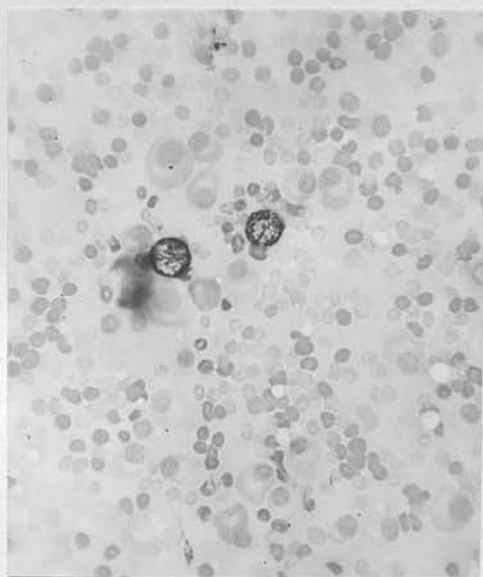
- Fig. 104: Sternal puncture. Bone marrow smear. A "pure culture" of myeloma cells - the result of the needle striking a nodule of myelomatous tissue. No other kind of marrow cells seen. x 300. Leishman.
- Fig. 105: High power of Fig. 104. Myeloma cells of plasmacytoma. One cell in mitosis. Observe the "hof", granular cytoplasm, eccentric nucleus and prominent nucleolus. x 800. Leishman.
- Fig. 106: Same marrow as in Figs. 104 and 105. The myeloma cells are peroxidase negative. Two peroxidase positive premyelocytes are shown for comparison in the centre of the field. x 300.
- Fig. 107: Myeloma cells stained by Unna Pappenheim stain. The cytoplasm is a granular pink and the "hof" is clear. There is no peculiar advantage in using this stain. x 300.
- Fig. 108: Sternal puncture. Bone marrow smear. Practically normal. Four myeloma cells are seen opposite the arrows. Such a finding requires a puncture in a different part of the sternum (c.f. Fig. 109). x 500. Leishman.
- Fig. 109: Sternal puncture. Bone marrow smear. Needle inserted one inch further up the sternum (c.f. Fig. 108). 65% myeloma cells present. There is now no doubt about the diagnosis. Figs. 108 and 109 show the different pictures which may be obtained from sternal puncture. One puncture may not be enough and the diagnosis may be missed. x 500. Leishman.



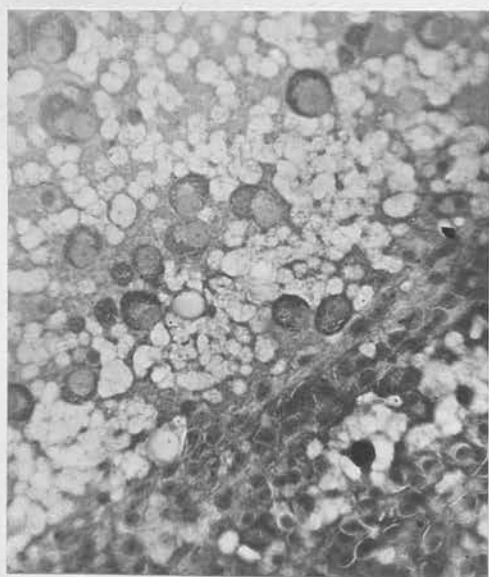
Case XIX, Fig. 104. x 300.



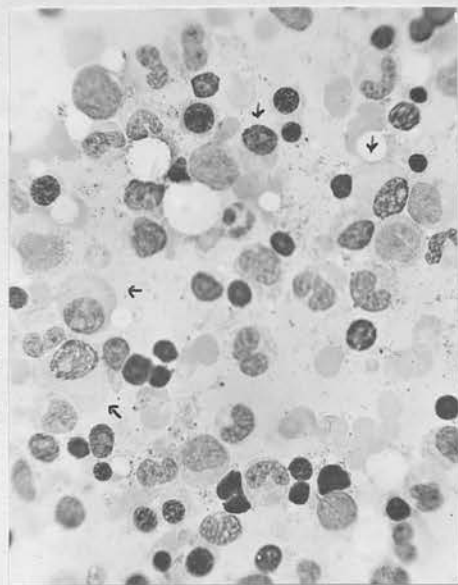
Case XIX, Fig. 105 x 800.



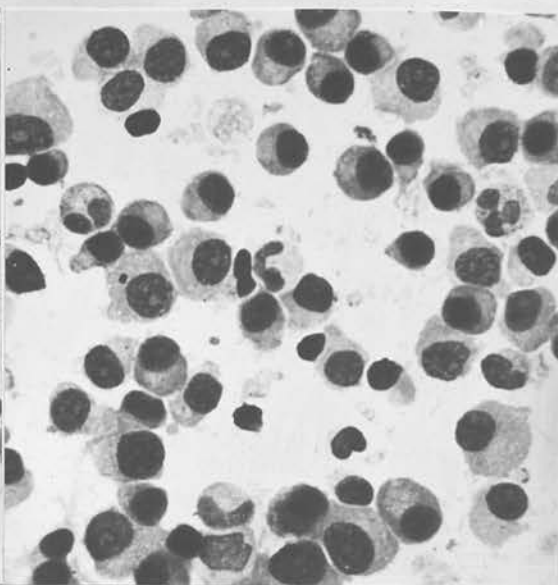
Case XIX, Fig. 106 x 300.



Case XIX, Fig. 107 x 300.



Case XX, Fig. 108 x 500



Case XX, Fig. 109 x 500



Fig. 110: X-ray of left femur. There is a fracture of the neck through a large cyst-like cavity growing from within. No other gross lesion was found in the skeleton by X-ray photography and yet the sternal puncture revealed the presence of large quantities of myeloma cells (c.f. Figs. 104-107). This is the kind of lesion that might be mistaken for a "solitary myeloma", disproved by sternal puncture.

Fig. 111: X-ray of thoracic vertebrae and ribs. The 6th vertebra is involved and there is fracture of the 10th left rib near its neck and also of the right 3rd rib, not shown clearly in the photograph.

Fig. 112: X-ray of pelvis. Area of bone destruction to the right ilium adjacent to the sacro-iliac joint.



Case XIX, Fig. 110.



Case XX, Fig. 111.



Case XX, Fig. 112.

Opposite p. 273.

Fig. 113: Biopsy left tonsil. Plasmacytoma.  
There is quite definitely a new growth,  
not just an infiltration of inflammatory  
plasma cells. The characteristic  
nucleus and cytoplasm are clearly seen.  
This is an example of the extramedullary  
plasmacytoma. x 350. H.E.

Fig. 114: Section of bone marrow (autopsy). The  
marrow is infiltrated by plasma cell  
myelomatous tissue. x 350.  
Heidenhain's iron haematoxylin.

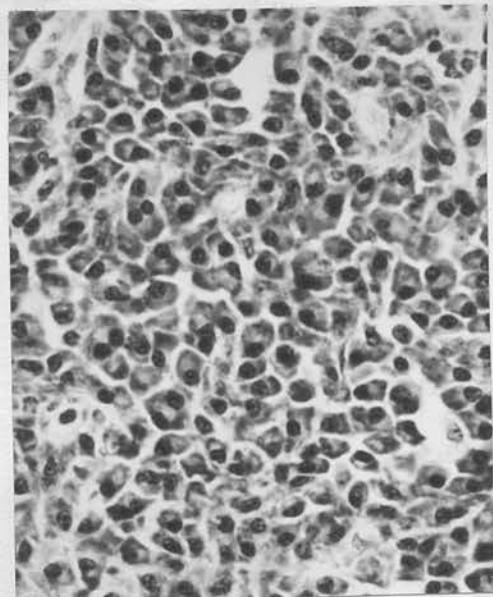
Fig. 115: Section of lymph gland. The sinuses  
contain histiocytes, lymphocytes and  
myeloma cells. x 350. H.E.

Fig. 116: Section of liver. Numerous myeloma  
cells in the liver sinusoids. It  
would be reasonable to assume that  
these cells were found in the  
peripheral blood. Notice that the  
distribution of the cells is very  
similar to that seen in myelogenous  
leukaemia. (c.f. Fig. 127). x 350.  
H.E.

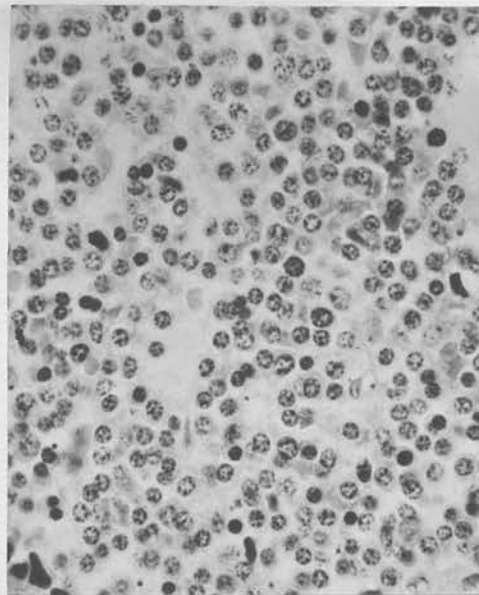
Fig. 117: High power of Fig. 116. Liver sinusoids  
packed with cells indistinguishable  
from myeloma cells (c.f. Fig. 114).  
From such a picture was made the as-  
sumption that in this case of  
myelomatosis a state of leukaemia  
existed. x 550. H.E.

Fig. 118: Section of Spleen. No tumour, but  
numerous leukaemic cells in the splenic  
sinusoids. These cells are in-  
distinguishable from myeloma cells.

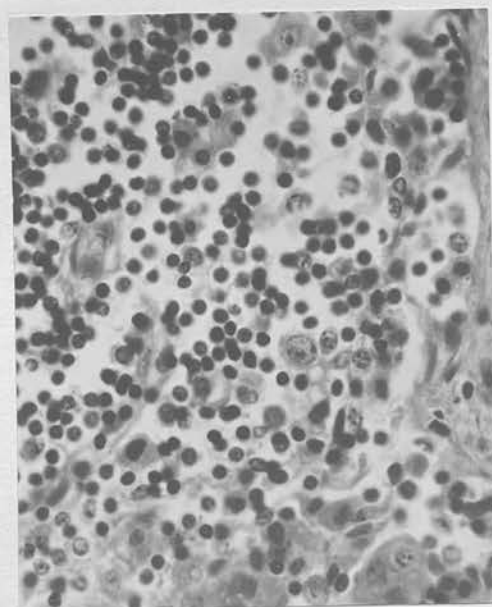




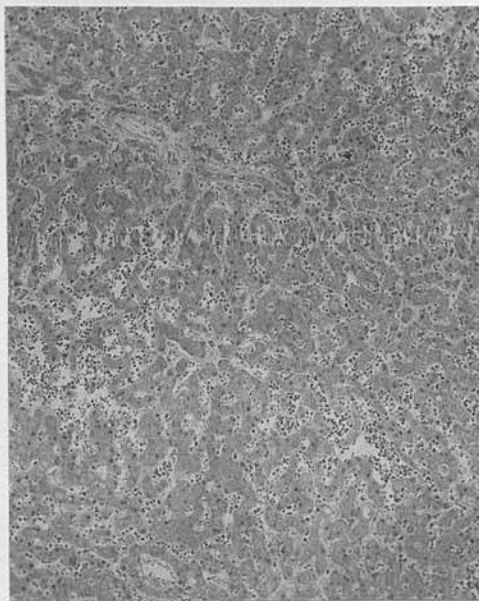
Case XXI, Fig. 113 x 350



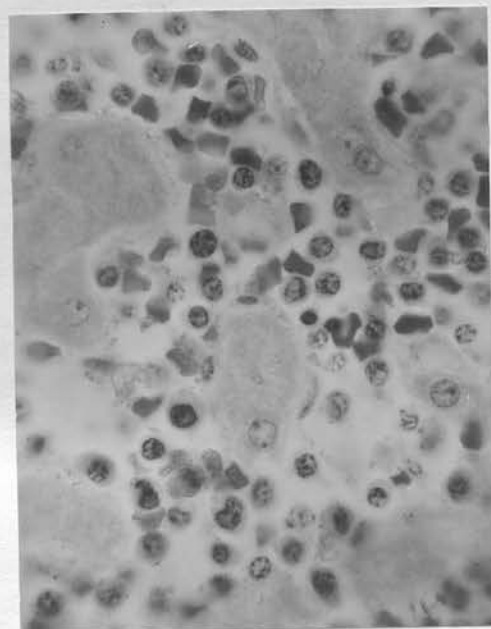
Case XXII, Fig. 114 x 350



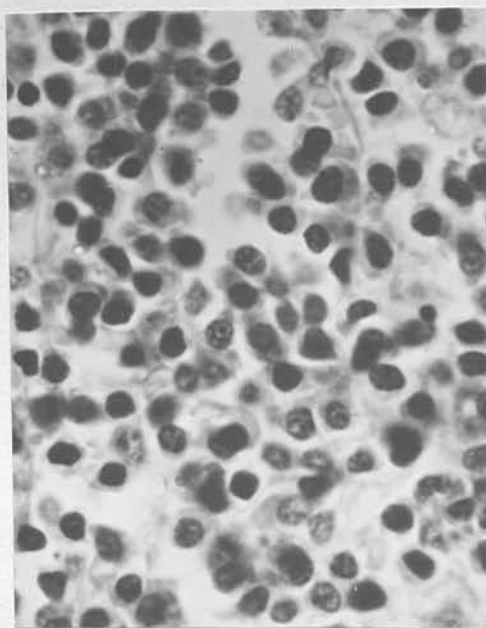
Case XXII, Fig. 115 x 350



Case XXII, Fig. 116 x 50



Case XXII, Fig. 117 x 550.



Case XXII, Fig. 118 x 500.

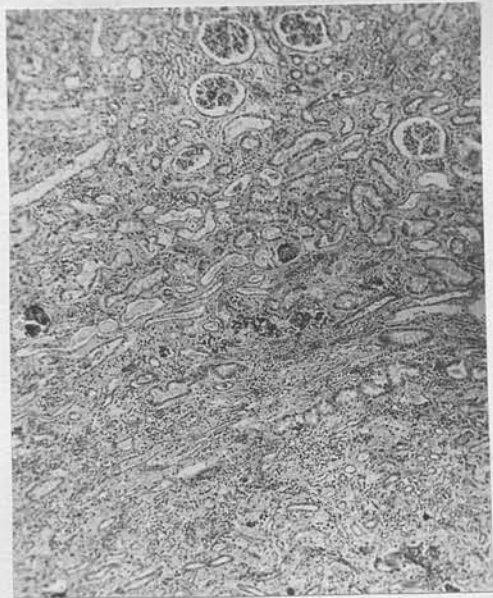
Opposite p. 274.

Fig. 119: Section of Kidney. There is calcification of the tubules, some fibrosis and a marked infiltration of cells which, under higher power, are indistinguishable from myeloma cells. x 50. H.E.

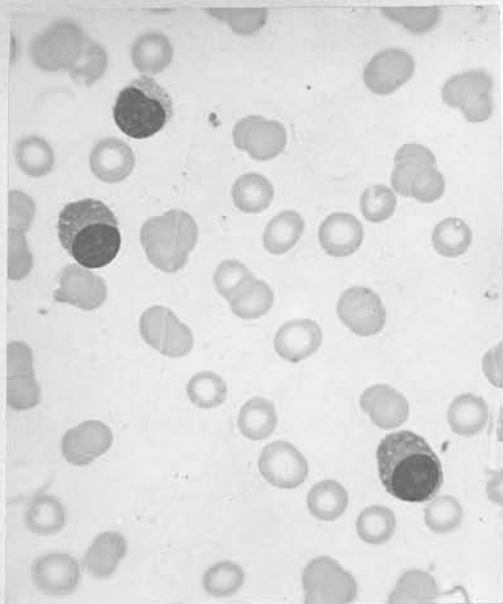
Fig. 120: Blood film showing Türk cells 39%. The cytoplasm is similar to that of the myeloma cell. There is no nucleolus as the Türk cell is an end cell. In this case there was autopsy proof of myelomatosis. x 650. Leishman.

Figs. 121-123: Three photographs of blood films taken from the same case, where apparently there was a state of leukaemia. Autopsy did not establish the presence of myelomatosis. (See comment in Case XXIV). Türk cells (T) are shown in comparison with lymphocytes, monocytes and leucocytes. There is a binucleated form in Fig. 123. The Türk cells stain darkly and are intensely basophil. x 650. Leishman.

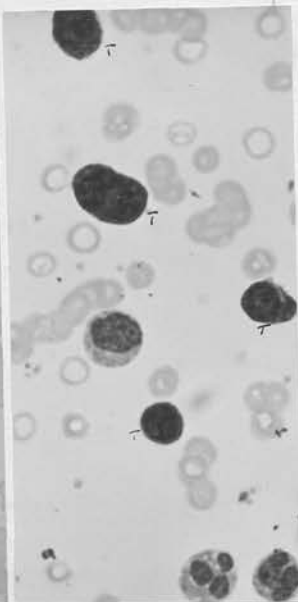
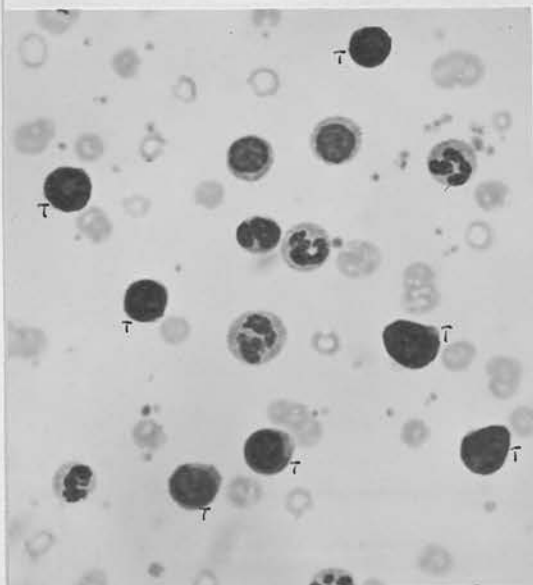
Fig. 124: The Türk cells are peroxidase negative. Two polymorphs are shown in comparison.



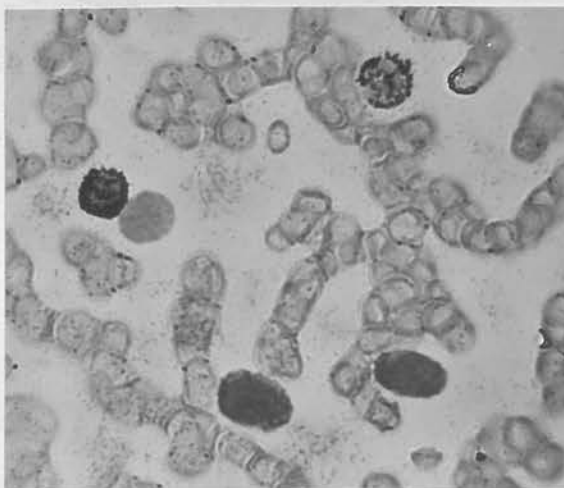
Case XXII, Fig. 119 x 50.



Case XXIII, Fig. 120 x 650



Case XXIV, Figs. 121, 122, 123, to show Turck cells (T) compared to lymphocytes, polymorphs and monocytes.



Case XXIV, Fig. 124 x 650.



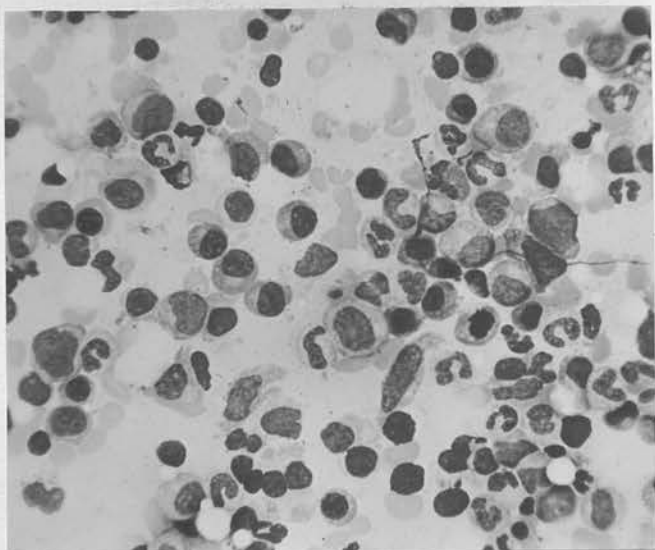
Fig. 125: Sternal puncture. Bone marrow smear.

The similarity between the pre-dominant cell, considered to be a plasma cell, and the plasmacytoma myeloma cell shown above is striking (c.f. Fig. 109). These plasma cells were peroxidase negative. x 400. Leishman.

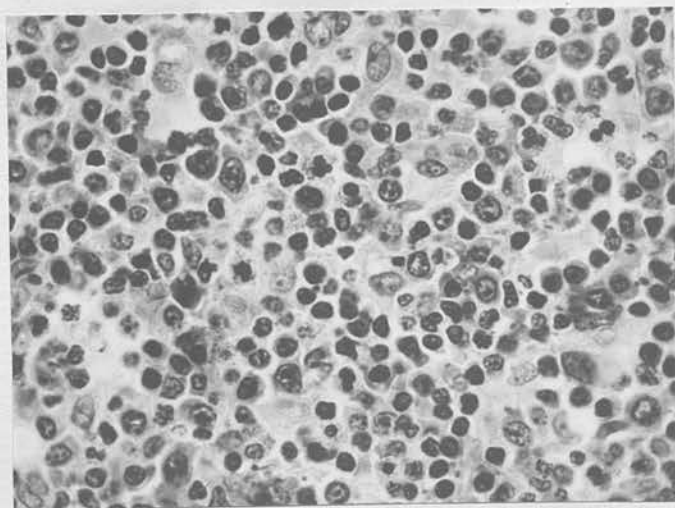
Fig. 126: Section of cervical lymph gland.

Biopsy. There is destruction of the normal architecture and a dense infiltration with plasma cells and some eosinophils. x 500. H.E.

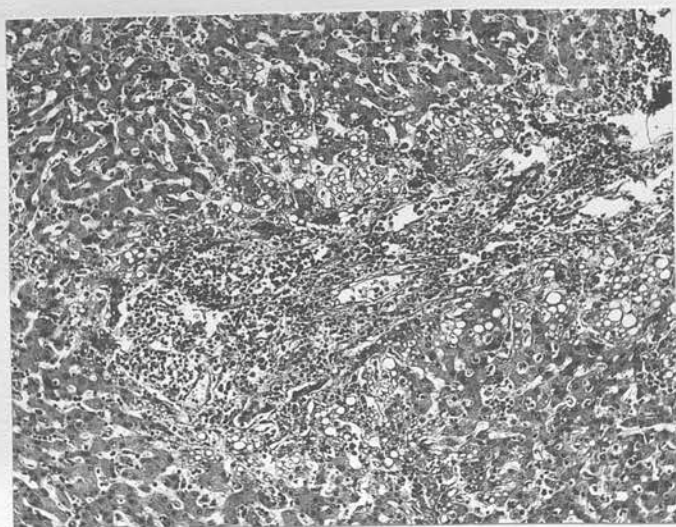
Fig. 127: Section of liver. Autopsy. The distribution of the leukaemic cells around the portal tract is similar to that seen in the typical lymphatic leukaemia (c.f. Fig. 116). x 200. H.E.



Case XXIV, Fig. 125 x 400.



Case XXIV, Fig. 126 x 500.



Case XXIV, Fig. 127 x 200.

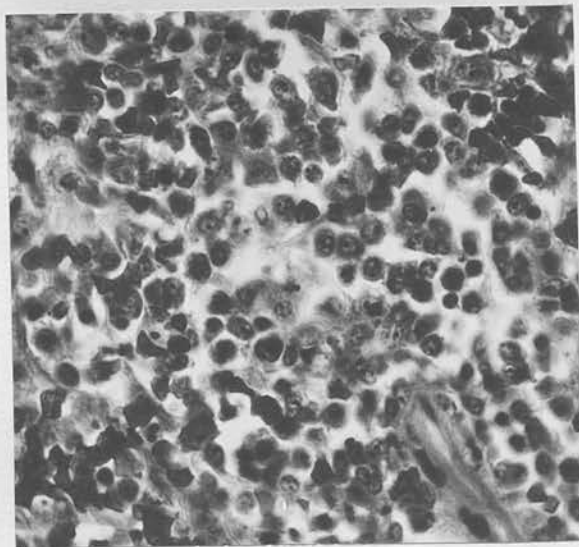
Fig. 128: Section of spleen. Autopsy. In-  
filtration of plasma cells similar  
to those seen in the section of the  
lymph gland (Fig. 126). x 500.  
H.E.

Fig. 129: Section of tumour in clavicle. Biopsy.  
This stain brings out the nucleoli in  
good contrast. All the nucleoli  
cannot be put into focus at the same  
time. The malignant cell here is  
much more like a myeloblast than a  
plasmacytoma cell. There is no "hof",  
and the cytoplasm is scanty. x 600.  
E.M.B.

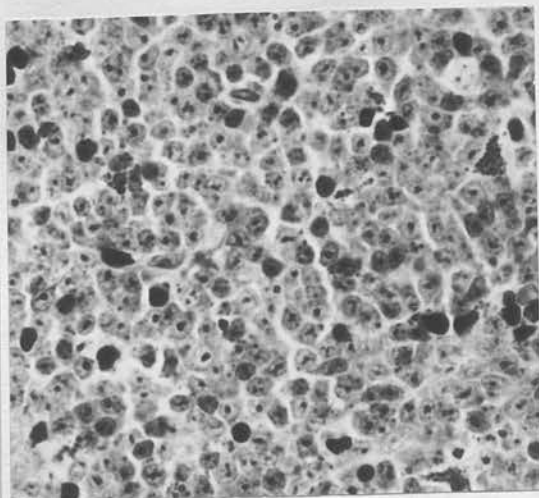
Fig. 130: Same tumour as above to show reticulum.  
x 300. Foot.

Fig. 131: Section of subcutaneous fat. Infiltration  
of myeloma cells similar in type to those  
seen in Fig. 129. x 60. H.E.

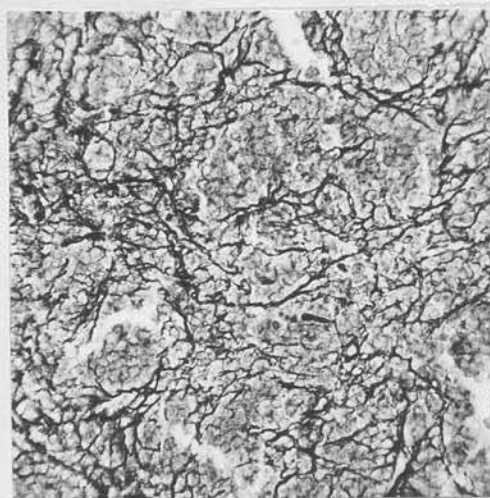




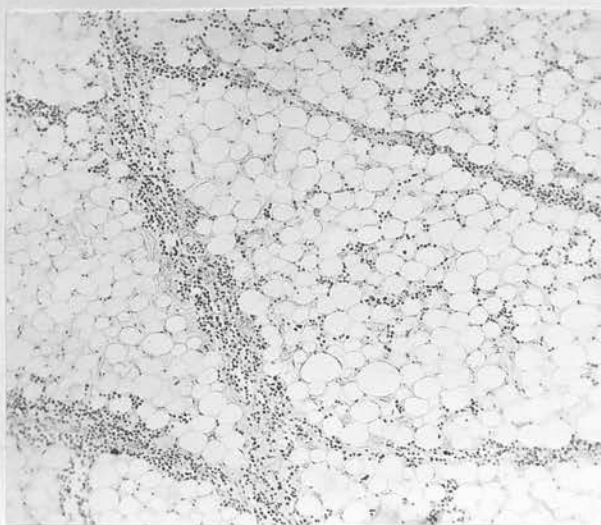
Case XXIV, Fig. 128 x 500.



Case XXV, Fig. 129 x 600.



Case XXV, Fig. 130 x 300.



Case XXV, Fig. 131 x 60.

Fig. 132: Lower power view of autopsy section of bone marrow from the femur. To the left is the myeloblastic infiltration, then only slightly increased marrow reaction, and to the right at P a marked aggregation of cells similar to plasma cells (see Fig. 133). x 7.  
E.M.B.

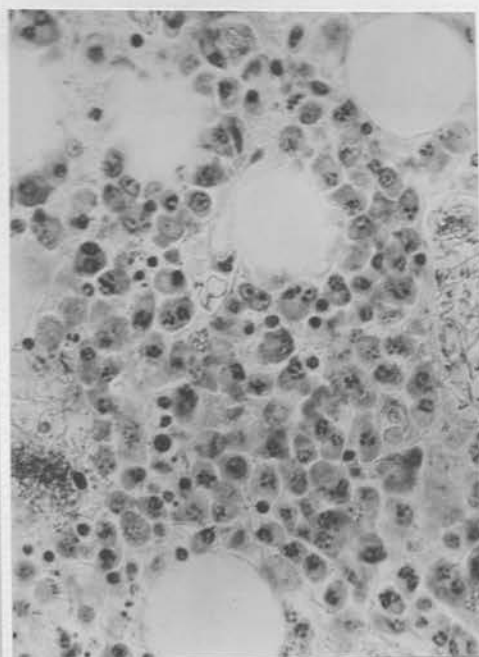
Fig. 133: High power of P, Fig. 132. These cells are all identical with plasma cells and their appearance seems to be in advance of the myeloblastic invasion (Fig. 134). It may be a defensive reaction on the part of the bone marrow plasma cell or possibly a modification of the malignant cell in this particular case. x 475.  
H.E.

Fig. 134: High power field of the marrow to the left in Fig. 132. These cells are indistinguishable from the myeloblasts of the ordinary myelogenous leukaemia and are quite different from the malignant cell of the plasmacytoma. It is doubtful if this case should be classified as a myeloma. It is probably a case of myelogenous leukaemia with chloromatous manifestations. x 475. H.E.

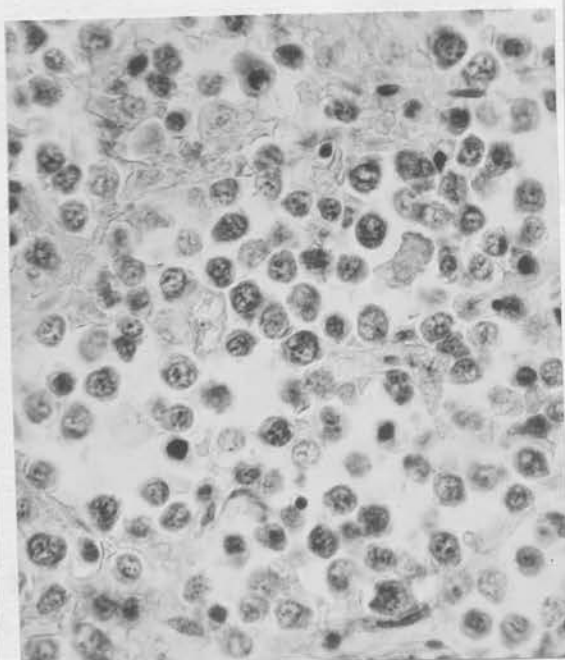
Fig. 135: Section of dura mater. Neoplastic tissue is adherent to the under surface. x 18.  
H.E.



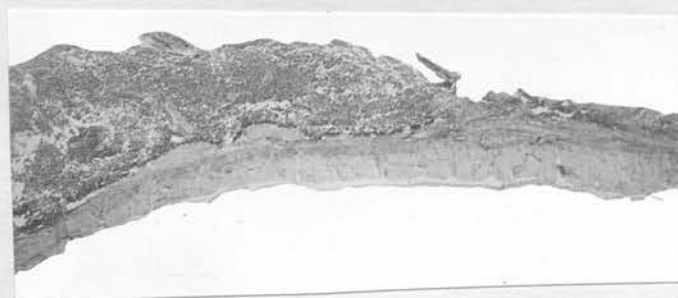
Case XXV, Fig. 132 x 7.



Case XXV, Fig. 133 x 475.



Case XXV, Fig. 134 x 475.



Case XXV, Fig. 135 x 18.

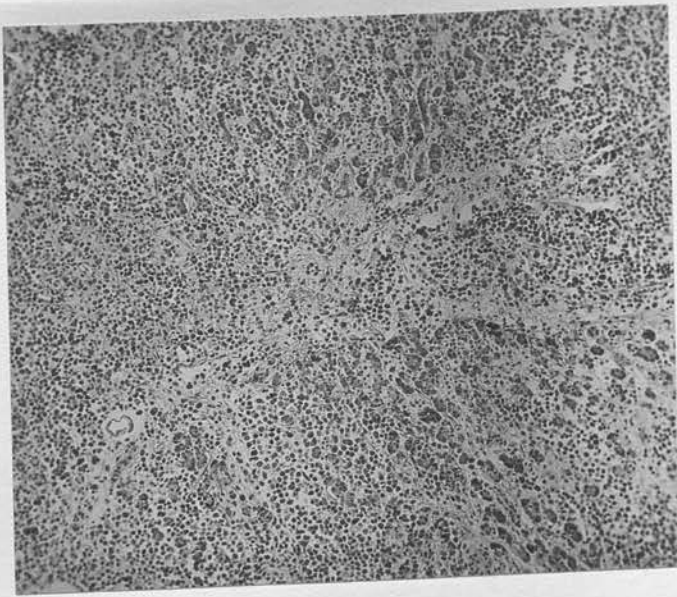


Opposite p. 278.

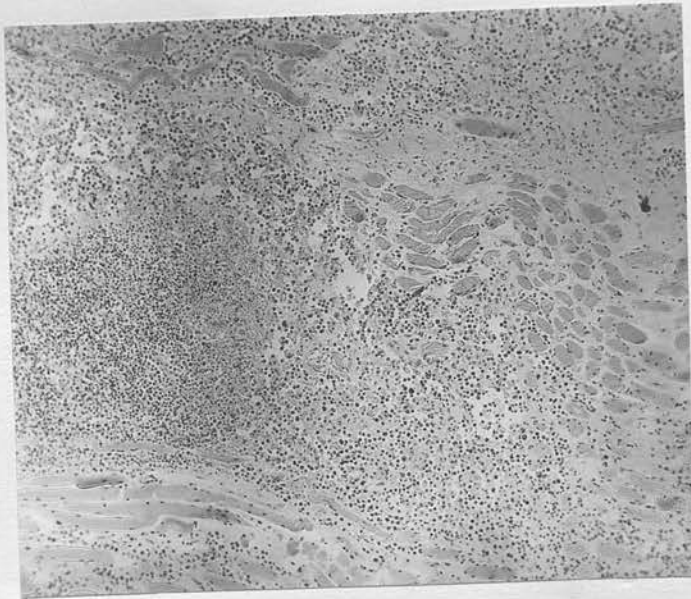
Fig. 136: Section of pancreas. Intense infiltration by myelomatous tissue.  
x 80. H.E.

Fig. 137: Section of skeletal muscle. The muscle fibres are isolated by the neoplastic tissue. x 65. H.E.

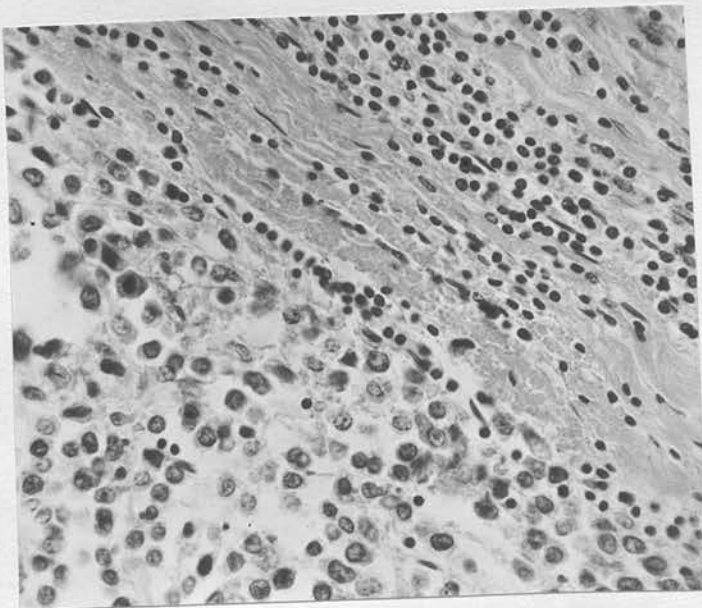
Fig. 138: Section of edge of growth in skeletal muscle. There is a plasma cell infiltration in the adjacent muscle. This is probably a non-specific reaction to the neoplasm. x 375.  
H.E.



Case XXV, Fig. 136 x 80.



Case XXV, Fig. 137 x 65.



Case XXV, Fig. 138 x 375.

Opposite p. 279.

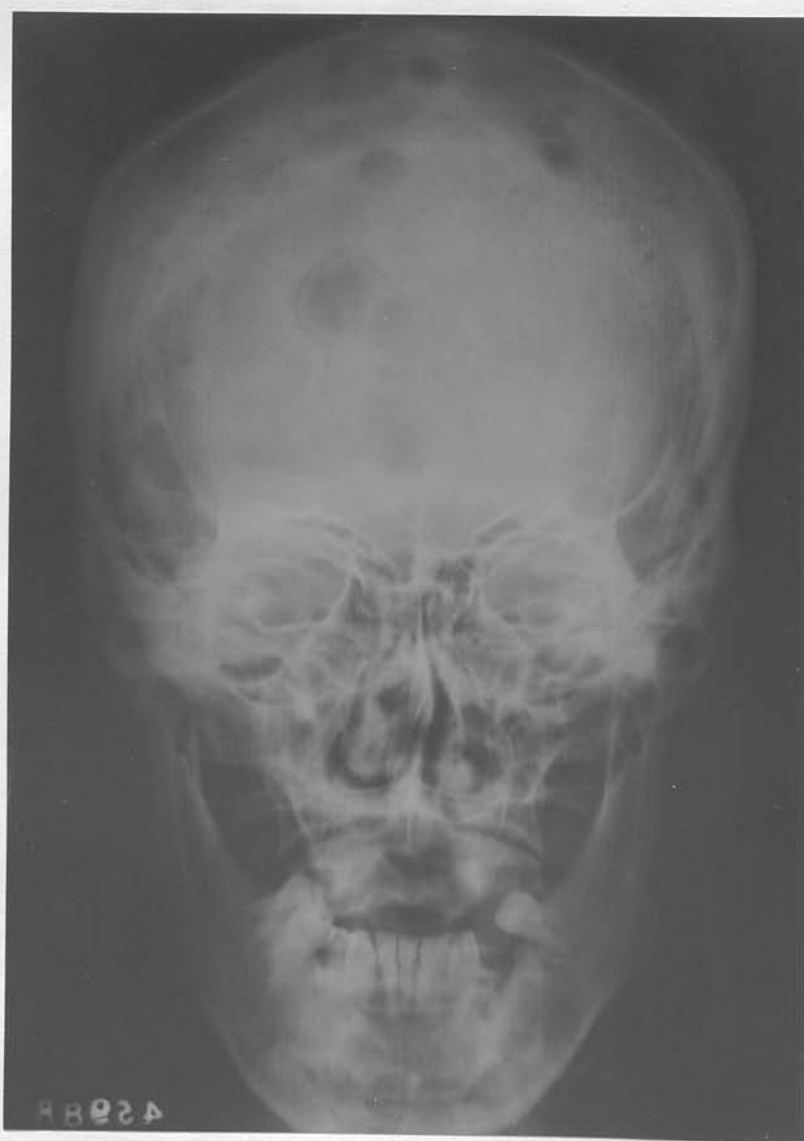
Figs. 139 & 140: X-ray photographs of the skull.

Several radiotranslucent areas  
in the vault.





Case XXV, Fig. 139.



Case XXV, Fig. 140.

Opposite p. 280.

Fig. 141: X-ray of right shoulder. Clavicle and acromion show medullary translucency. The outer end of the clavicle is swollen.

Fig. 142: X-ray of sternum showing "egg-shell" bone. Both anterior and posterior aspects of bone are wavy.



Case XXV, Fig. 141.

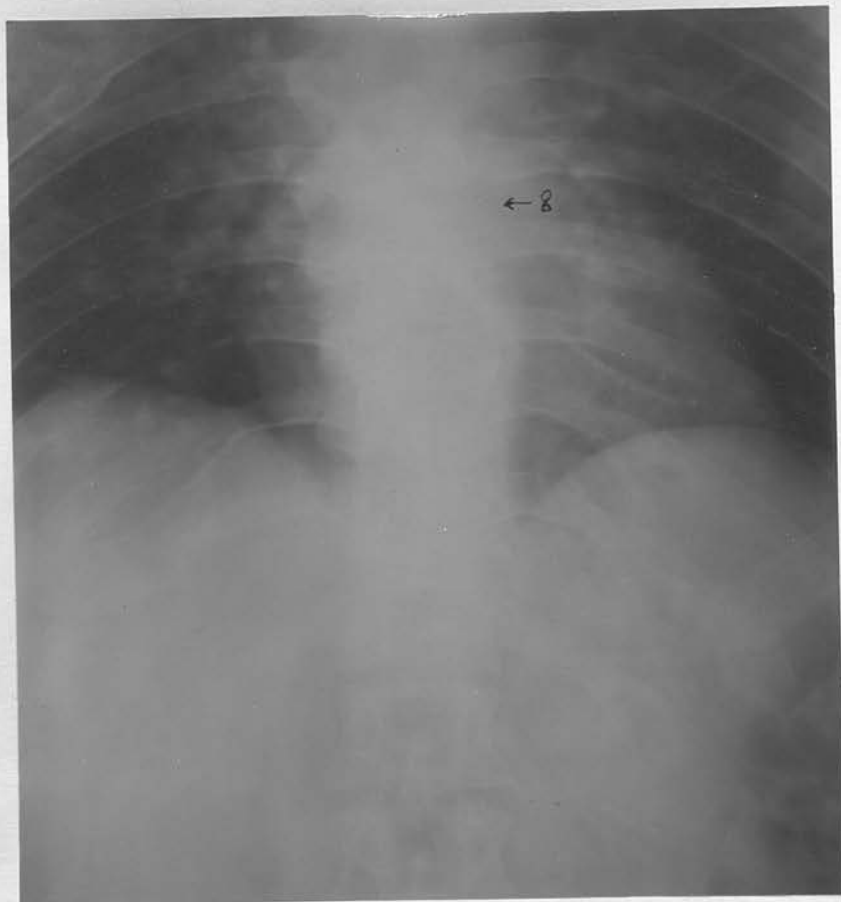


Case XXV, Fig. 142.



Fig. 143: X-ray of lower thorax. All the ribs are rarefied and myelomatous. There is partial collapse of the 8th dorsal vertebra. Obvious changes are seen in the 5th, 9th, 10th and 11th ribs on the right side and the 6th, 8th, 11th and 12th on the left. Spontaneous fractures have occurred in 5th and 9th ribs on the right side.

Fig. 144: X-ray of pelvis. Both iliac bones show large tumours.



Case XXV, Fig. 143.



Case XXV, Fig. 144.

Opposite p. 282.

Fig. 145: X-ray of right forearm. Some  
rarefaction and periosteal thickening.

Fig. 146: X-ray photographs of autopsy specimens  
of right clavicle and sternum to  
show more clearly the extent of bony  
destruction.

Figs. 147 & 148: X-rays of autopsy specimens of  
the heads of the femora.  
Early destructive changes.





Case XXV, Fig. 145



Case XXV, Fig. 146.



Case XXV, Fig. 147.



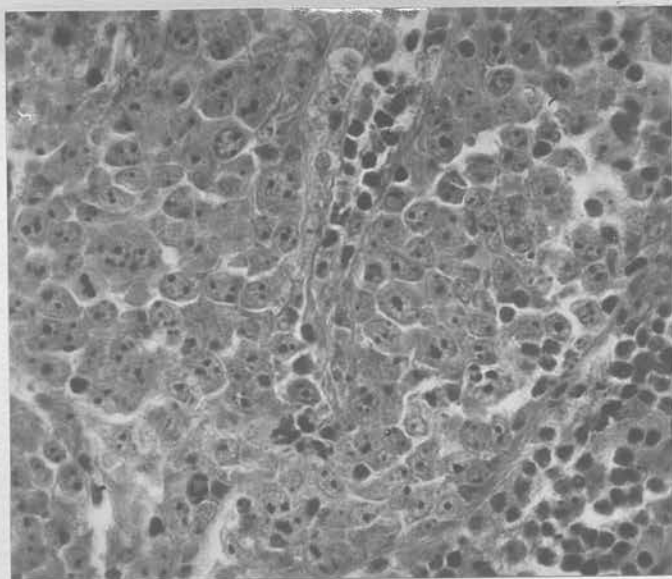
Case XXV, Fig. 148.

Opposite p. 283.

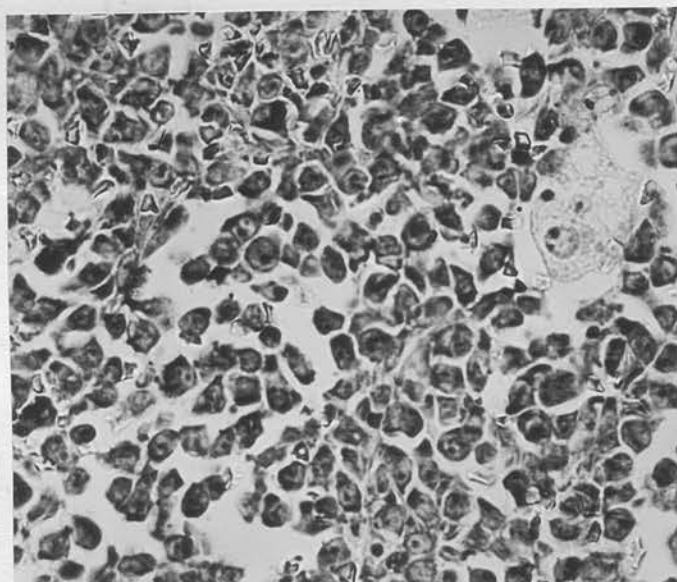
Fig. 149: Section of tumour in anterior superior iliac spine. Biopsy. The cells are similar to myeloblasts. They have not the appearance of plasmacytoma myeloma cells. The presence of more than one nucleolus is clear. It is of course debatable whether these "nucleoli" are such and not chromatin nodes with similar staining reactions surrounding one nucleolus. The latter suggestion is probably the more accurate. The point is that more than one of such bodies is not found in the plasmacytoma cell. The majority of the cells have no "hof" but there are a few cells present indistinguishable from plasmacytoma cells. x 500. H.E.

Fig. 150: Section of tumour behind the ear. Biopsy. The tumour cell here is much more like the myeloblast than the "plasma cell" of myeloma. x 500. H.E.

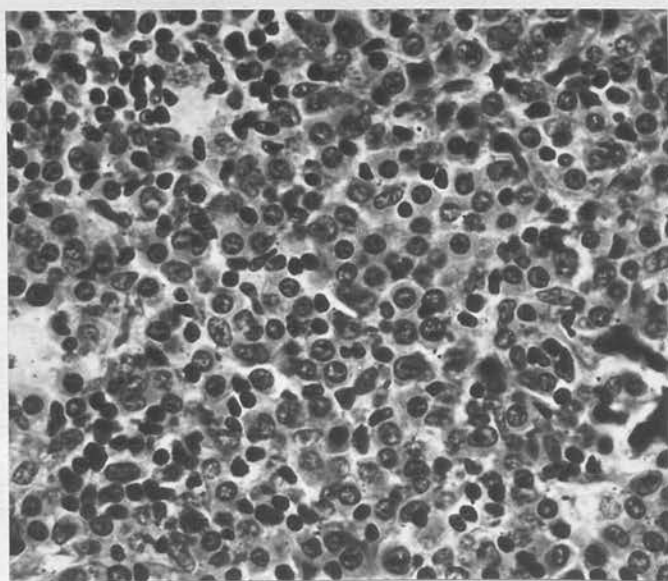
Fig. 151: Section of bone marrow. Femur. Autopsy. The tumour cell is similar to a myelocyte. This was claimed to be a myelocytic myeloma. This is doubtful. It is probably a leukaemia with chloromatous manifestations. x 500. H.E.



Case XXVI, Fig. 149 x 500.



Case XXVII, Fig. 150 x 500.



Case XXVIII, Fig. 151 x 500.



Opposite p. 284.

Fig. 152: X-ray of skull. Multiple radio-translucent areas.

Fig. 153: X-ray of lower dorsal vertebrae and ribs and lumbar vertebrae.  
Rarefaction in vertebrae and ribs  
and collapse of 4th lumbar vertebra.



Case XXIX, Fig. 152.



Case XXIX, Fig. 153.

Opposite p. 285.

Fig. 154: X-ray of pelvis, small multiple radiotranslucent areas.

Fig. 155: X-ray of left humerus. Multiple round punched out areas throughout the medulla, the shaft and the head.

Fig. 156: X-ray of lower cervical and upper dorsal vertebrae. There are many small radiotranslucent areas.





Case XXIX, Fig. 154.



Case XXX, Fig. 155.



Case XXX, Fig. 156.

Opposite p. 286.

Fig. 157: Lateral view of cervical spine (c.f. Fig. 156). Typical appearance of the multiple lesion of myelomatosis of the vertebrae.

Fig. 158: X-ray of lumbar vertebrae. There is rarefaction and expansion of the nucleus polposus. The nodularity is difficult to see in this reproduction.

Fig. 159: X-ray of right shoulder. Clavicle, scapula, humerus and ribs are all involved. The lesions are almost entirely medullary.

Fig. 160: X-ray of lumbar spine.



Case XXX, Fig. 157.



Case XXX, Fig. 158.



Case XXX, Fig. 159.



Case XXXI, Fig. 160.



Fig. 161: X-ray of cervical vertebrae. There is destruction of the lower part of the 2nd cervical vertebra. This at first was thought to be a giant cell tumour, but later photographs of the left humerus and femur and the sternum showed osteoporosis and some bony expansion. On this discovery the diagnosis of multiple myeloma was made.

Fig. 162: X-ray of thoracic spine. There is widespread involvement of vertebrae and ribs. The body of the 6th dorsal vertebra has collapsed.

Fig. 163: X-ray of pelvis and femoral heads. Innumerable small deposits in all bones.



Case XXXI, Fig. 161.



Case XXXII, Fig. 162.



Case XXXII , Fig. 163.

Fig. 164: X-ray of thorax in a case of adenocarcinomatosis of the skeleton. The ribs and clavicles have almost identical lesions to those seen in myelomatosis. A biopsy of a rib finally ruled out myelomatosis.

Fig. 165: A closer view of clavicles, ribs and vertebrae. The appearance is almost indistinguishable from that of myelomatosis.





Case XXXIII, Fig. 164.



Case XXXIII, Fig. 165.

Opposite p. 289.

Figs. 166 & 167: X-ray photographs of right and left ischia and femora. The medullary lesion growing from within is strikingly similar to that of myelomatosis.

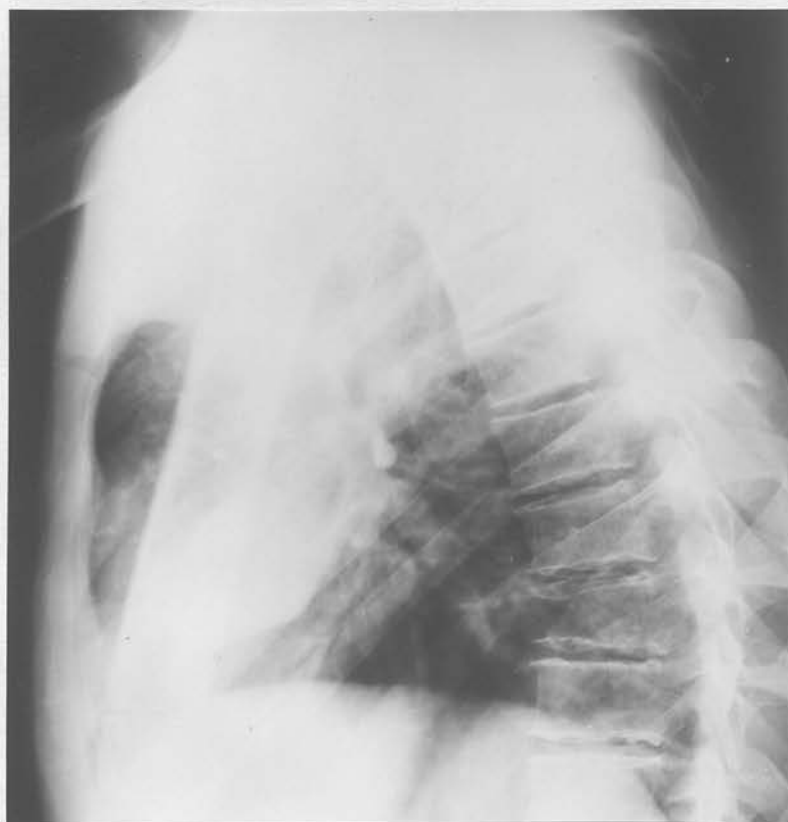
Fig. 168: Lateral view of thorax in case of bronchial carcinoma with metastasis to bone. The 5th, 7th and 8th ribs on the left side posteriorly were diseased.



Case XXXIII, Fig. 166.



Case XXXIII, Fig. 167.



Case XXXIV, Fig. 168.



Opposite p. 290.

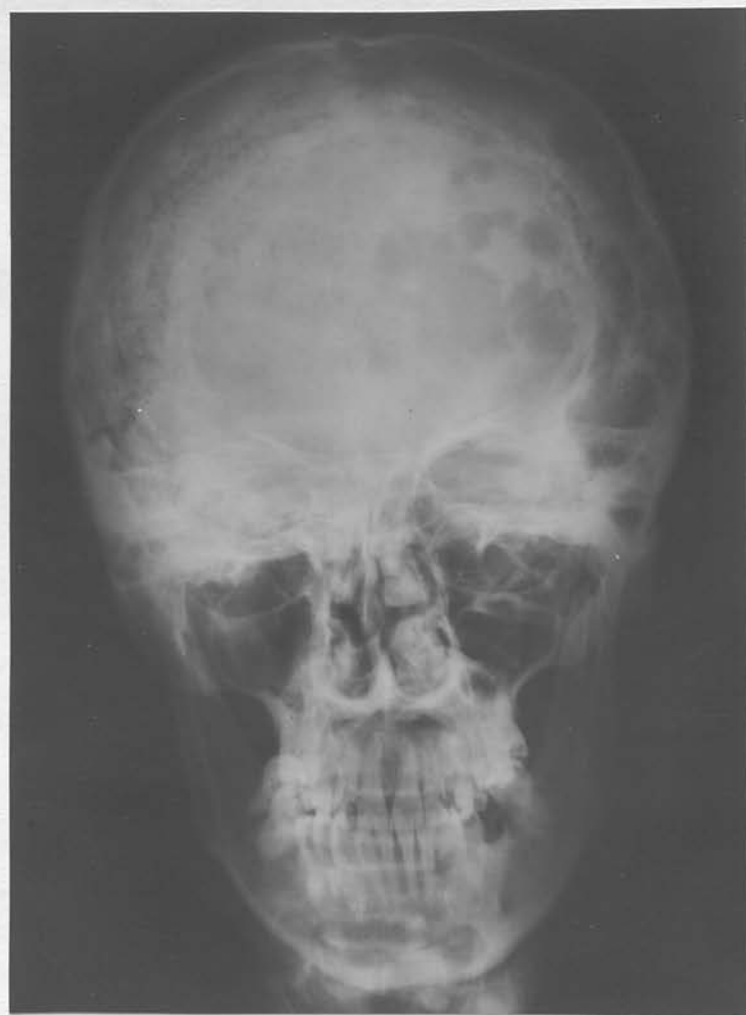
Figs. 169 & 170: X-ray photographs of the skull.

Bronchial carcinoma. A close study of the individual lesion will show that it lacks the clear punched out appearance so characteristic of myeloma. The edge here is less distinct.

These pictures are quite typical of carcinomatosis of the skull (c.f. Figs. 75 and 101).



Case XXXIV, Fig. 169.



Case XXXIV, Fig. 170.

Opposite p. 291.

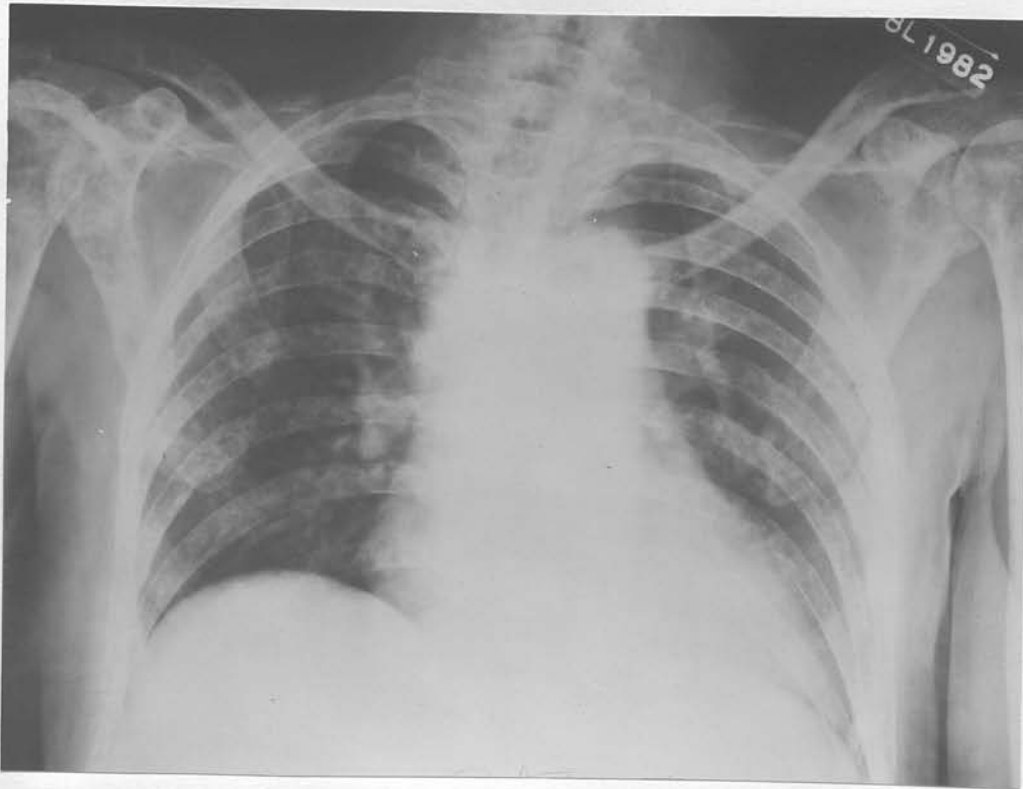
Fig. 171: X-ray of pelvis. There are areas of destruction in the right ilium and the right pubo-ischial ramus. There is also destruction in the upper ends of the femora (c.f. Figs. 93, 103, 112).

Fig. 172: X-ray of thorax in case of skeletal carcinomatosis, primary in the right breast. Scapulae, humeri, clavicles and ribs all show multiple lesions. The picture is not unlike myelomatosis (c.f. Figs. 76, 77, 141 and 165).





Case XXXIV, Fig. 171.



Case XXXV, Fig. 172

Opposite p. 292.

Figs. 173 & 174: X-rays of thoracic and lumbar vertebrae clearly showing multiple metastatic foci not unlike myelomatosis.

Fig. 175: X-ray of pelvis. Multiple foci similar to myelomatosis.

In these photographs there is less osteoporosis and there is some bony reaction to practically every nodule (c.f. Figs. 81, 82, 83, 84, 95, 96, 97 and 102).



Case XXXV, Fig. 173.



Case XXXV, Fig. 174.



CaseXXXV, Fig. 175.



Opposite p. 293.

Figs. 176 & 177: X-ray photographs of the skull.

Carcinoma of the breast.

(c.f. Figs. 169 and 170).



Case XXXV, Fig. 176.



Case XXXV, Fig. 177.

Opposite p. 294.

Fig. 178: X-rays of the femora. Metastatic  
invasion of the medulla. (c.f.  
Figs. 91, 92, 94, 166 and 167).







Case XXXV, Fig. 178.